Vol. 36 No. 189 October, 1961

ARCHIVES OF DISEASE IN CHILDHOOD

EDITORS
I. A. B. CATHIE and RICHARD H. DOBBS

THE JOHN CREAR LIBRARY
NOV 21 1961

CONTENTS

	PAGE
Hyperplasia of the Adrenal Medulla in Hypertension of Children. DORA BIALESTOCK	465
The Myenteric Plexus in Infantile Hypertrophic Pyloric Stenosis. J. R. RINTOUL and N. F. KIRKMAN	474
Sex-linked Hydrocephalus. J. H. EDWARDS, R. M. NORMAN and J. M. ROBERTS	481
The Syndrome of Sex-linked Hydrocephalus. J. H. EDWARDS	486
Haemolytic Anaemia in Osteopetrosis—A Report of Two Cases. H. GAMSU, J. LORBER and JOHN RENDLE-SHORT	494
A Haemolytic-uraemic Syndrome in Infancy. JOAN GRIFFITHS and K. G. IRVING	500
Foetal Haemoglobin in Haemolytic Disease of the Newborn. THOMAS E. OPPÉ and IAN D. FRASER	507
Infantile Congenital Aneutrocytosis. DAGFINN AARSKOG	511
A Longitudinal Study of the Growth and Development of Prematurely and Maturely Born Children, Part VIII. CECIL MARY DRILLIEN	515
Cephalic Spread of Neuroblastomas in Children. W. I. B. ONUIGBO	526
Tuberculosis in B.C.G. Vaccinated Children in Singapore. FREDA M. PAUL	530
Studies in the Physiology of Sweating in Cystic Fibrosis. II: Elevated Night Sweating Rates. MAARTEN S. SIBINGA and GIULIO J. BARBERO	537
Hypophosphatasia: A Genetic Study. J. C. RATHBUN, J. W. MACDONALD, H. M. C. ROBINSON and J. M. WANKLIN	540
Hypernatraemic Dehydration in Infantile Gastro-enteritis. DUNCAN MACAULAY and MARGARET I. BLACKHALL	543
Myocarditis and Croup Caused by Coxsackie Virus Type B5. JUDITH M. BABB, MARGARET E. R. STONEMAN and H. STERN	551
Contusion of the Lung in Childhood. A. SCHWARTZ and J. B. BORMAN	557
Osteomyelitis of the Premaxilla. E. C. ALLIBONE and C. P. MILLS	562
An Unusual Aortic Aneurysm in an Infant. A. M. WOMACK and B. WOLMAN	565
A Rare Type of Congenital Cyanotic Heart Disease. PATRICIA FERNANDO and M. V. F. PERERA	569
Book Reviews	573

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

YEARLY SUBSCRIPTION (6 NUMBERS) £4 4s. 0d. U.S.A. $13.50 SINGLE NUMBER 17s. 6d.

EDITORIAL COMMITTEE

J. Apley
P. T. Bray
W. M. Dennison
Isabella Forshall
Douglas Gairdner
J. L. Henderson
Hugh Jolly
F. F. Kane
Clifford Parsons
Winifred Young

President of the British Paediatric Association
Editor, *British Medical Journal*

Appointed by the British Paediatric Association and the British Medical Association

NOTICE TO CONTRIBUTORS

Papers for publication should be sent to the Editors, B.M.A. House, Tavistock Square, London, W.C.1.

Submission of a paper for publication will be held to imply that it contains original work which has not been previously published. Permission to republish must be obtained from the Editors.

Papers should be as concise as possible and illustrations kept to the minimum. Manuscripts should be typewritten top copies in double spacing. They should have been carefully revised, and alterations in proof apart from printers' errors are not permissible.

Photographs and photomicrographs should be submitted unmounted. Drawings and diagrams should be boldly drawn in black ink on stout white paper. Any necessary lettering may be lightly inserted in pencil.

Overseas contributors should nominate somebody resident in Great Britain willing to correct their proofs and deal with the subject of reprints.

Current numbers of the *Archives of Disease in Childhood* should be consulted for information concerning standard abbreviations, etc. In references to papers in the text the year of publication in parenthesis should follow the author's name. References at the end of the text should be in alphabetical order of author's names, and titles of journals should be abbreviated according to the *World List of Scientific Periodicals*. **Titles of articles should be included; if this is not done papers will be returned to their authors for completion.** Book titles should be followed by the place of publication.

Failure to observe the above directions will lead to delay in publication.

Fifty reprints are supplied free. Further reprints must be ordered when returning proofs.

Subscription. £4 4s. 0d. per annum, post free.

Applications for advertising space should be made to the Advertisement Manager, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

When you can almost see them grow...

During the years of rapid growth and development, heavy demands are made on the physical and nervous energies of children. It is important to ensure that their weight and strength keep pace with their increasing inches.

'Ovaltine' provides a useful dietary reinforcement for growing children. It is a nutritious food beverage made from malt, milk, cocoa, soya and eggs, and fortified with extra vitamins. Delicious and easily digested, 'Ovaltine' helps to build up health, strength and energy, and to maintain normal weight increase. It is also of value for those recovering from the common fevers of childhood.

You can confidently recommend 'Ovaltine' to supplement the diet of growing children.

OVALTINE

VITAMIN STANDARDIZATION PER OZ. Vitamin B_1, 0.3 mg.; Vitamin D, 350 i.u.; Niacin, 2 mg.

A. WANDER LIMITED · 42 UPPER GROSVENOR STREET · LONDON W.1

Factory, Farms and 'Ovaltine' Research Laboratories: King's Langley, Herts. M422

GENERAL PRACTICE PROVES BROXIL THE MOST EFFECTIVE ORAL PENICILLIN

AVAILABLE IN TABLET AND SYRUP FORM

Broxil (Regd) is a product of British Research at the Beecham Research Laboratories Ltd., Brentford, England. Tel: ISLeworth 4111

PARENTROVITE IN GENERAL PRACTICE

Parentrovite, a high potency injectable preparation of the vitamin B complex with vitamin C, is being found of increasing usefulness in general practice. Introduced originally for the treatment of acute psychiatric emergencies such as coma or delirium from alcohol or drug overdosage, it has since been found to be of much wider application for conditions not uncommonly met in patients being nursed in their own homes. Many a patient can now, with appropriate dosage, be kept at home instead of having to be admitted to a general or a mental hospital.

The formula is based on the fact that normal cerebral function depends on the oxidation of glucose and that any interference with the underlying biochemical mechanisms can cause symptoms of mental disturbance. Severe infections, burns, trauma, surgical operations and "stresses" of all kinds can be as potent as drugs and alcohol in causing interference with the enzyme systems responsible for glucose oxidation and resultant failure of return to health.

To reverse such changes and to restore normal cerebral function, massive doses of the B vitamins and ascorbic acid are needed—doses out of all proportion to normal nutritional needs. The vitamins are used here not as nutrients but as potent drugs employed pharmacologically.

Conditions Reported Responsive to Parentrovite

The after-effects of influenza, pneumonia and other severe infections,
Post-operative depression and confusion,
Debility with loss of memory in old people,
Alcoholism, acute and chronic,
Habituation to barbiturates.

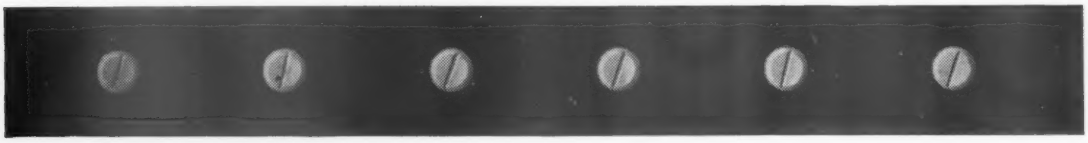
Parentrovite

PACKS: in boxes of 3 and 12 pairs. Hospital pack also available.

NATIONAL HEALTH SERVICE
In no case is the cost of a V.L. preparation greater than, and in some it is less than, that of the official equivalent preparation. There is no official equivalent of some V.L. specialities.

VITAMINS LIMITED, UPPER MALL, LONDON, W.6.

a fresh start in corticosteroid therapy



βetnelan

the entirely new anti-inflammatory steroid

Betnelan names betamethasone, an entirely new compound developed in Britain by Glaxo Laboratories Ltd. It is effective in low doses in **acute asthma, severe eczema, severe allergic urticaria, shock** and other conditions for which corticosteroids are indicated systemically.
Betnelan is devoid of salt retention activity, has negligible effect on potassium balance, causes no mental depression, has no muscle weakening effect and shows promise of clinical superiority in other respects.

Each tablet of Betnelan contains 0·5 milligram betamethasone and for short-term therapy a "**2:1:½**" dosage scheme is suggested. For example, **2** tablets t.i.d. for 2 days followed by **1** tablet t.i.d. for 2 days and ½ tablet t.i.d. for 2 days.

For maintenance, dosage need be no more than ½ tablet twice daily.

The merits of betamethasone derive from its unique chemical structure formed by introducing a methyl group, (CH_3), in the beta position on the molecule of 9-fluoro prednisolone. This represents more than 20 new stages of manufacturing complexity.

...and Betnelan is inexpensive

GLAXO

GLAXO LABORATORIES LIMITED

in a single dose . . .

comprehensive vitamin supplementation

ABIDEC* DROPS (providing vitamins *A*, *C* and *D* with members of the vitamin *B* complex) are formulated to supply in a single dose the daily vitamin requirements of the average child. ABIDEC is instantly miscible with milk, purees or other foods.

ABIDEC CAPSULES, in a single daily dose of one capsule, provide the approximate daily requirements of seven essential vitamins for older children and adults.

ABIDEC

PARKE-DAVIS

Abidec Drops in bottles of 10 ml. and 50 ml. each with dropper.
Abidec Capsules in bottles of 30 and 250 capsules.

*Trade Mark

PARKE, DAVIS & COMPANY · HOUNSLOW · MIDDLESEX · TEL.: HOUNSLOW 2361
Inc. USA Liability Limited

WPS

for the combination
of broad spectrum effectiveness...
taste... convenience
of dosage... protection
against yeast overgrowth...
UNMATCHED BY ANY OTHER
BROAD SPECTRUM ANTIBIOTIC
PREPARATION.

MYSTECLIN-F

Squibb Phosphate—Potentiated Tetracycline plus Amphotericin—B (FUNGIZONE)

FOR SYRUP ... FOR PAEDIATRIC DROPS

tetracycline therapy at its best ...
plus the new *antifungal antibiotic,*
Fungizone, to prevent fungal
superinfection.

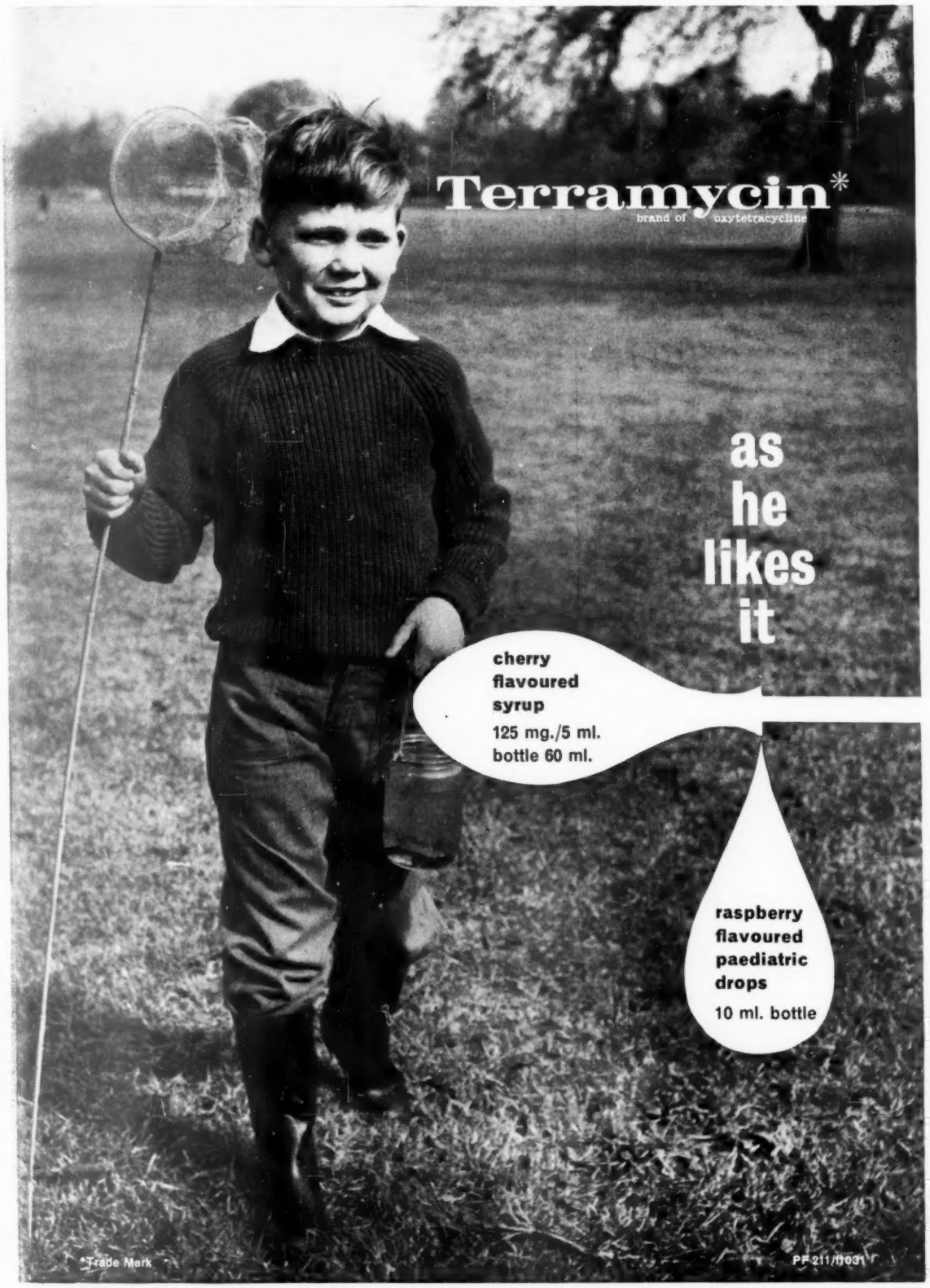
When reconstituted, the syrup provides a fruit-flavoured aqueous suspension containing 125 mg. tetracycline (HCl equiv.) and 25 mg. Fungizone per 5 ml. teaspoonful. Supplied in bottles for reconstitution to 60 ml. The drops when reconstituted provide 100 mg. tetracycline (HCl equiv.) and 20 mg. Fungizone per ml. Supplied with unbreakable plastic dropper in bottles for reconstitution to 10 ml.

SQUIBB

A century of experience builds faith

E R SQUIBB & SONS LTD Edwards Lane Speke Liverpool 24

'Mysteclin' and 'Fungizone' are trademarks



Pfizer SCIENCE FOR THE WORLD'S WELL-BEING Pfizer Ltd · Sandwich · Kent

...and for your

normal babies too!

HYPERPLASIA OF THE ADRENAL MEDULLA IN HYPERTENSION OF CHILDREN

BY

DORA BIALESTOCK

From the Department of Surgical Research, Royal Children's Hospital, Melbourne, Victoria, Australia

(RECEIVED FOR PUBLICATION MARCH 24, 1961)

Persistently high blood pressure is rare in childhood and warrants detailed investigation. Reviews on this subject by McCrory and Nash (1952) and Daeschner and Dodge (1959) have included extensive discussion of hormonal factors and adrenal tumours, but they make no mention of adrenal medullary hyperplasia.

Adrenal medullary hyperplasia was found on histological examination in two children with hypertension. In the absence of a definitive medullary tumour and with negative tests for phaeochromocytoma, hyperplasia may play an important role in the production of the hyperpiesia. The study of these two cases, and of one additional unproven case, forms the basis of this paper.

In one of these cases, G.P., microdissection techniques were used to study the nephron morphology and special histological techniques to study the juxtaglomerular body in an attempt to locate the site or origin of the renal pressor substance.

Material and Methods

To obtain perspective regarding the incidence of cases of adrenal medullary hyperplasia, case histories of all patients admitted to the Royal Children's Hospital over a seven-year period (1952-1959) and classified under hypertension without nephritis or cardiovascular disease, were studied, and subdivided on an aetiological basis. Two patients who had been investigated at the Royal Children's Hospital died, and autopsies were undertaken. These were G.P., male, aged 5 years, and F.M., male, aged 11 years. A third child, S.W., female, aged 12 years, whose clinical features fit the pattern of the two histologically proven cases died and no autopsy was performed.

The three special features which were observed histologically were the adrenal medullae, the nephrons and the juxtaglomerular apparatus of Goormaghtigh (1939). The adrenal medullae were stained with haematoxylin and eosin, the juxtaglomerular apparatus by Bowie's stain (1936) modified by Pitcock and Hartroft (1958). The nephrons were studied by the technique of microdissection (Oliver, MacDowell and Tracy, 1951; Ritchie and Waugh, 1957).

An approximate quantitative assessment of the increase in the size of the cells of the adrenal medullae was obtained by measuring 100 cells and their nuclei. The large vacuolated cells with oval eccentric nuclei were measured (Drake, Hibbard and Hellwig, 1944). Measurements from the two cases studied were compared with average measurements from three normal cases in their respective age groups. One control specimen was obtained from a case of chronic nephritis with moderate hypertension. Measurements in this case were the same as for the other two controls of the same age. No other adrenals from hypertensive children were available for study.

Pitcock's stain was used on two normal kidneys from children aged 5 years, to compare and contrast the effect of the stain with the abnormal kidneys. Nephron dissection of a comparable normal kidney from a 5-year-old child was also undertaken for comparison with observations on the abnormal.

Case Reports

Case 1.—G.P., male, aged 5 years, with adrenal medullary hyperplasia with renal disease.

Four months after his family had emigrated to Australia from Italy, G.P., a boy of 4 years, first presented at the Royal Children's Hospital, Melbourne. He was an only child, and two years before sailing for Australia, he suddenly developed a left facial paresis. This gradually improved, but was still present on his arrival in Australia. During the voyage he had been increasingly lethargic. His appetite was poor. He developed intense thirst with profuse sweats, especially at nights, when he needed two pints of fluid. He passed urine two or three times every night; there were no other urinary symptoms. There were no items of relevance in the family history.

On examination he was a small, thin, sallow boy (weight 28 lb.) with a left facial paresis and a blood pressure of 260/175 mm. Hg, a large heart, with triple rhythm and systolic and diastolic bruits. His femoral pulses were easily palpable. Temperature 99·6° F.; pulse rate 100/minute. The liver edge was palpable; his limbs were hypotonic. The fundi were pale, but there was no papilloedema or exudate. He showed persistent variable albuminuria. Urinary concentration tests showed a variation in specific gravity from 1,015

FIG. 1.—Posterior surface of right kidney of Case 1. The granular zone on this surface around the hilum was supplied by a normal calibre vessel. The rest of the kidney seen in this picture was smooth surfaced, a dusky blue and supplied by small abnormal vessels.

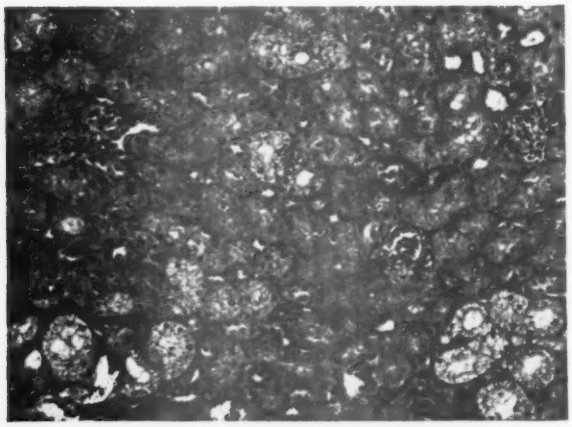


FIG. 2.—Section from the right kidney (Case 1) in the zone supplied by small abnormal vessels Note the absence of fibrosis between the nephrons. The tubular cells show severe degenerative changes. There is no cellular infiltration. (× 95.)

to 1,018. On microscopy the urine contained granular and hyaline casts but no abnormal cells. Blood urea levels fluctuated between 30 mg./100 ml. and 60 mg./100 ml. Full blood examination, serum proteins and electrolyte pattern and electrophoresis pattern were all normal. Urinary pressor amine tests were normal. The intravenous pyelogram was normal. Aortography revealed renal angiograms which indicated a more rapid and dense blush on the left than on the right side. Both sides finally exhibited good renal iodide density.

While in hospital *Proteus* was cultured from his urine. This infection was controlled with 'furadantin' (nitrofurantoin). Twelve days later, after a short course of 'ansolysen' (pentolinium), 'serpasil' (reserpine), 'chlotride' (chlorothiazide) and nitrofurantoin his blood pressure fluctuated between 270/170 and 300/200 mm. Hg.

Urinary pressor amine tests repeated three times were all normal. He was sent home on antihypertensives, diuretics and mandelix, as organisms cultured this time from his urine were insensitive to other antibiotics.

For the next three months he remained symptom free. He then developed abdominal pain, anorexia, rapid heart action and a cough. He was passing urine three or four times each night. He developed gross dyspnoea and congestive cardiac failure. His blood pressure was 285/190 mm. Hg. Urine contained protein, and *Proteus* was cultured. Microscopy showed granular and hyaline casts. The blood urea was 44 mg./100 ml.

The urinary potassium excretion on normal and low potassium diets was normal. Urinary ketosteroid and corticosteroid estimations were normal. In view of the normal electrolyte pattern and normal potassium excretion, the estimation of aldosterone in the urine was considered unnecessary.

Abdominal aortogram performed via the right femoral artery, revealed a normal left renal artery and abnormally small right renal artery. The right renal outline was also smaller than the left.

Howard's test (Howard, Berthrong, Gould and Yendt, 1954) for the water and salt was marred by technical difficulties.

Mainly on the findings of the second aortogram, right nephrectomy was performed. After operation, the blood pressure fell from 300/170 to 260/140 mm. Hg in the first post-operative week. Over the next few weeks his general condition progressively deteriorated, and he developed severe epistaxis, acidosis and uraemia. The blood urea rose from 96 mg./100 ml. in the first post-operative week to 815 mg./100 ml. just before death four weeks later.

The right kidney (45 g.) removed at operation, was normal in shape and slightly smaller than normal in size, (normal: 65 g.). Most of the kidney was a dusky grey-blue colour and was supplied by three abnormally small branches of the anterior division of the right renal artery, each about 1 mm. in diameter. The posterior branch of the right renal artery was normal in calibre, measuring about 3 mm. in diameter. Two raised, coarsely granular areas of normal coloured kidney tissue lay on the posterior surface of the kidney immediately around the hilum and at the upper pole of the kidney (Fig. 1). These two parts were supplied by normal calibre vessels, one the posterior division of the right renal artery and the other, an accessory branch arising from the right suprarenal artery. There were no subcapsular adhesions. The cortico-medullary demarcation was indistinct. The renal pelvis was normal.

Histologically most of this kidney, i.e. those parts probably supplied by the extremely small calibre vessels, showed crowding of glomeruli and tubules which were normal or slightly smaller than normal in size. There was no increase of interstitial tissue and no cellular infiltration. Cell outlines were indistinct and nuclei, especially of tubule cells, were poorly defined (Fig. 2).

No thickened arterioles were seen. The histology of those parts of the right kidney supplied by the normal calibre vessels was similar to that of the left kidney and will be described in the post-mortem report.

Autopsy. The body was that of an emaciated olive-skinned 5-year-old boy with a right nephrectomy scar.

Relevant observations included a grossly enlarged heart, with maximum thickening of the left ventricle. Lungs were congested. All other organs except the kidneys and suprarenals were macroscopically and microscopically normal, except for occasional small haemorrhages. No extrarenal chromaffin tissue could be found in the neck, the peritoneal cavity or retroperitoneal tissues.

The left kidney weighed 60 g. (Fig. 3) and was normal in size and shape, though the surface was grossly congested and mottled with deep purplish-blue areas and large pale patches. The surface was smooth and the capsule stripped with ease. Section revealed poor cortico-medullary demarcation.

Microscopic changes throughout the left kidney were the same as those in the two small areas in the right kidney. There was a gross derangement of renal pattern, with hypertrophy of tubules and some glomeruli which exhibited fibrous obliteration of Bowman's space and of the capillaries. There was a generalized increase in interstitial fibrous tissue with moderate infiltration by small round cells (Figs. 4 and 5). Both the intima and medial coats of the arterioles were grossly thickened. In some, there was complete obliteration of the lumen (Fig. 5). There was no histological evidence of renal dysplasia (Ericsson and Ivemark, 1958).

These histological features reveal a severe grade of chronic pyelonephritis and arteriolar thickening.

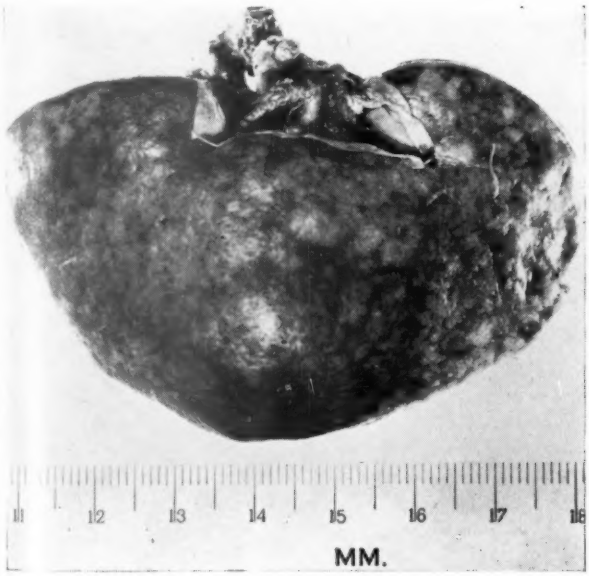


FIG. 3.—Granular mottled surface of left kidney (Case 1). This granularity was similar to that seen in those parts of the right kidney supplied by normal calibre blood vessels.

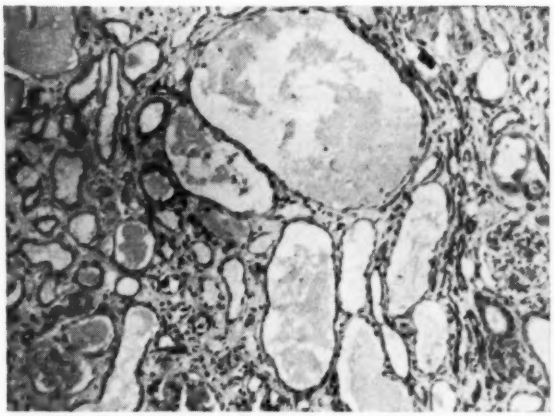


FIG. 4.—Left kidney (Case 1) gross tubular hypertrophy separated by increased fibrous tissue. These grossly hypertrophic tubules probably form the isolated cystic structures seen by the microdissection in Figs. 7 and 8. (× 95.)

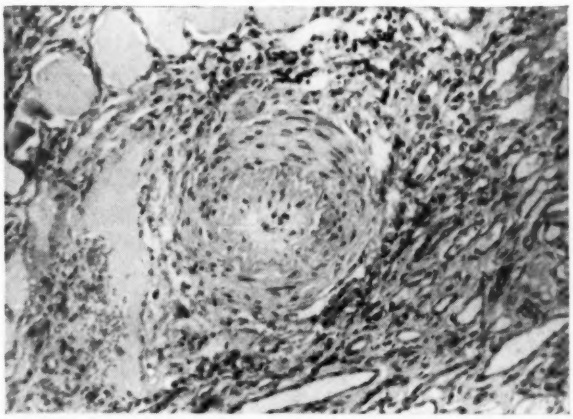


FIG. 5.—An obliterated arteriole amongst hypertrophic and atrophic tubules separated by increased fibrous tissue from the left kidney (Case 1). (× 95.)

Microdissection was carried out on the left and right kidneys, together with dissection of a normal kidney (Table 1). Nephrons in most of the right kidney were small, but the morphology was otherwise normal. In the left kidney and those parts of the right kidney supplied by normal calibre vessels there was great variability of size of glomeruli and tubules; hypertrophic elements were more frequent than small atrophic nephrons; in this kidney a number of blind-ending cystic structures occurred predominantly in areas of dense fibrous connective tissue, probably representing parts of hypertrophic tubules sequestrated by the inflammatory process. These occurred only in areas of scarring (Figs. 6 and 7). Several times during the dissection a discrete group of cells intimately connected with the afferent arteriole at the vascular pole of the glomerulus was isolated. This probably corresponds to the juxtaglomerular apparatus of Goormaghtigh (Fig. 8).

Pitcock's stain gave a good demonstration of the cells

TABLE 1

DIAMETER OF NEPHRONS FROM CASE 1 AND FROM NORMAL KIDNEY OF CORRESPONDING AGE

Case	Glomerulus (μ)	Proximal Tubule (μ)	Loop of Henle		Distal Tubule (μ)	Collecting Tubules (μ)
			Narrow (μ)	Wide (μ)		
Normal 5-year-old	150	40	25	40	40	Not recorded
Case 1: right kidney ..	120	65	25	40	30	Not recorded
Case 1: left kidney ..	170	85	Not recorded	Not recorded	90	40–65 to 130

Figures obtained from average of 50 measurements.

of the juxtaglomerular apparatus of Goormaghtigh in all kidneys examined. These cells were seen best in association with the subcapsular glomeruli in the outer rim of the cortex. In the left kidney and those parts of the right kidney supplied by normal calibre vessels the juxtaglomerular cells were filled with dense basophilic granules. Granules with the same dense blue colour were also seen in the hypertrophic tubules in the same vascular distribution (Fig. 9). If, as has been suggested, these granules are the source of the renal pressor substance, then the tubule epithelium and the juxtaglomerular cells would both be involved in this case.

FIGS. 6 and 7.—Microdissection of the left kidney (Case 1), showing two isolated cysts terminating blindly. (× 50.)

In summary, the two kidneys present the following features: The left kidney and those parts of the right kidney supplied by normal calibre arteries exhibit severe chronic pyelonephritis with gross thickening and obliteration of intrarenal arterioles. The juxtaglomerular apparatus is readily identified because of the dense granules in the cells. The remaining nephrons exhibit a mixture of hypertrophy and atrophy. The hypertrophic nephrons are the more numerous. The changes in the dusky right kidney were minimal. No abnormal features were found in the parenchyma apart from a very slight generalized diminution in size of the nephrons. The blood vessels were not thickened and the juxtaglomerular apparatus was identified but contained no granules.

The suprarenal glands were not weighed, but they appeared macroscopically normal.

Microscopically the cortex was normal with all zones well defined. The medulla contained far more cellular tissue than is usually observed. Sheets of cells arranged

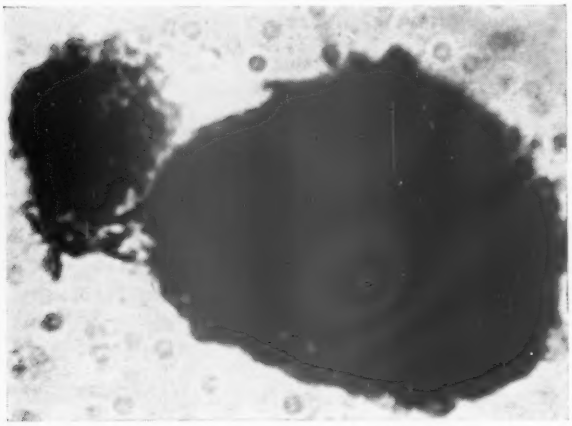


FIG. 8.—Microdissection of a glomerulus with an afferent arteriole and a group of cells attached at the upper pole. This represents an example of the juxtaglomerular apparatus in the left kidney (Case 1). (× 550.)

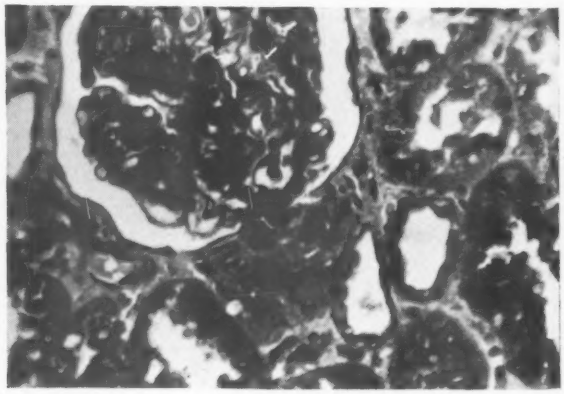


FIG. 9.—The juxtaglomerular apparatus (Pitcock's stain) seen in section in left kidney (Case 1). Dense granules can be seen in these cells, but also in the hypertrophic tubules at the right lower corner. (× 448.)

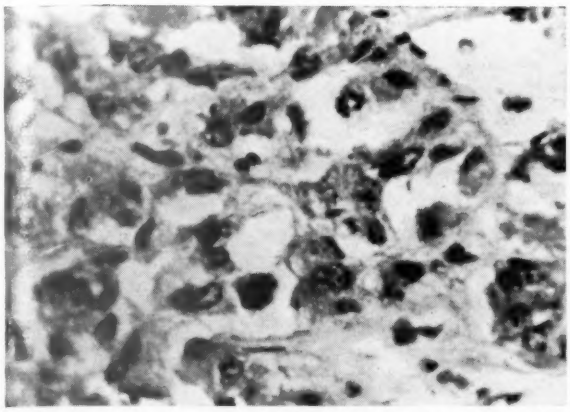


FIG. 10.—Section from the medulla (Case 1). Note the cellular pleomorphism. Most of the cells are large and oval with eccentric, pale nuclei with vacuoles and nucleoli. Note the mitotic figure at the upper right-hand side of the photomicrograph. (× 448.)

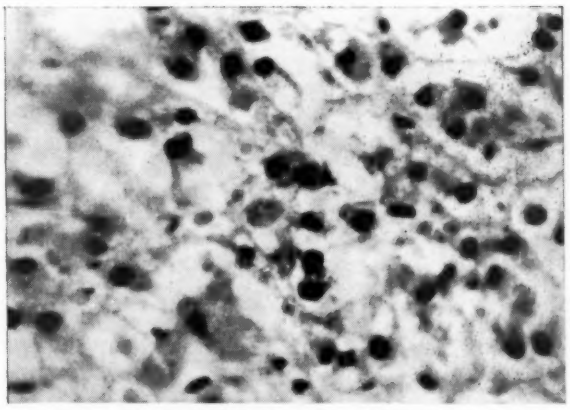


FIG. 11.—From the medulla of a 5-year-old control. The cells are far more uniform, smaller with round dark nuclei and there are no mitotic figures. (× 476.)

in cords and vesicles surrounded dilated sinusoids. Increase in bulk of the medullary tissue was due to proliferation of large vacuolated eosinophilic pleomorphic cells. Their nuclei were pale, oval, eccentrically placed, and contained nucleoli and mitotic figures (Figs. 10 and 11). One hundred such cells and their nuclei were measured. The large medullary cells in three sections from children of the same age were also measured and the average figures obtained are recorded in Table 2. The medullary cells in Case 1 were much larger than those of the controls and the nuclei were twice the normal size.

Case 2. F.M., male, aged 11 years, with adrenal medullary hyperplasia.

In this second case hyperplasia of the adrenal medulla without any other lesion was found. The child died shortly after admission, and for this reason his condition was incompletely investigated.

He had complained of numerous headaches in the past 18 months. These had become particularly severe in the week before admission to hospital. There was nothing relevant in his past history, and his family history revealed no features of relevance to this study.

Six hours before admission his headache had become worse, he had vomited, become stuporose and gradually lost consciousness.

When examined, the child was semicomatose and very restless—blood pressure 250/180 mm. Hg, femoral pulses were easily palpable and physical examination revealed no abnormality. Reflexes were all present and active, his plantar responses were extensor and his fundi exhibited papilloedema but no exudates. A ventriculogram suggested a possible block in the Aqueduct of Sylvius. Craniotomy and exploration of the posterior fossa were performed but revealed no cause for the raised intracranial pressure.

Urine was normal to ward tests and on microscopy, blood urea estimation was 43 mg./100 ml. He died without appreciable change in his condition 19 hours after admission.

Autopsy. The heart was grossly enlarged with thickening predominantly of the wall of the left ventricle. The aqueduct was not stenosed. Apart from these features, the vascular, respiratory, digestive, reticuloendothelial and central nervous systems were normal.

The genito-urinary system was normal. Both kidneys were of normal size (right 83 g. and left 78 g.), their capsules stripped readily and on section the appearance was that of normal renal architecture. Pelvis, ureters and bladder were all normal in size. The bladder was thin-walled and clear urine could be expressed readily through the urethra. Histologically, glomeruli, tubules and interstitial tissues were normal. Arterioles were thickened.

A thorough search was made for extra-adrenal chromaffin tissue, but no tumour of this nature could be found. Regions examined included the entire peritoneal cavity and the retroperitoneal tissues. The neck was explored to exclude a carotid body tumour. None was found.

The adrenals each weighed 4 g. and appeared normal to the naked eye. Other endocrine glands were macroscopically and histologically normal. Microscopically the changes in the adrenals were very similar to those described in Case 1. Cortex was normal with all layers well defined. The medulla appeared to be more cellular than usual with the increase in volume again due to

TABLE 2

MEASUREMENTS OF CELLS OF MEDULLA OF SUPRARENAL GLANDS

Case	Medullary Cells (μ)	Nuclei (μ)	Mitotic Figures
Case 1:			
Age 5 years	18	10	Present
5-year-old controls (3 cases) ..	12	5	Absent
Case 2:			
Age 11 years	16	9	Absent
11-year-old controls (3 cases)	10	5	Absent

TABLE 3

ANALYSIS OF 20 CASES OF HYPERTENSION
(GLOMERULONEPHRITIS AND CARDIOVASCULAR DISEASE EXCLUDED)

Diagnosis	No. of Cases	Sex	Comment
Adrenal medullary hyperplasia (Case 1 and Case 2)	2	Male	Severe hypertension, one case with associated renal disease, the other without any other lesion
Diagnosis uncertain, possibly medullary hyperplasia (Case S.W.)	1	Female	An 11-year-old girl presented with a four months' history of severe headaches. Blood pressure 200/140 mm. Hg. Repeated urine microscopy revealed no abnormality and concentration power was up to 1,032; Hb normal; repeated regitine tests and estimations of urinary pressor amines gave normal results; one urea clearance test gave 55% of normal clearance; blood urea estimations fluctuated between 34 mg./100 ml. and 64 mg./100 ml.; an intravenous pyelogram showed normal kidneys and an aortogram revealed a normal renal vascular pattern. A diagnosis of chronic nephritis was made. The child died at home with renal failure two years later; no autopsy was performed
Phaeochromocytoma	3	Male	Severe hypertension; two cured by removal of the tumour; one died of secondary deposits with severe hypertension
Unilateral renal disease	4	3 male 1 female	Moderate hypertension; blood pressure in the three males became normal after unilateral nephrectomy; in the female, the blood pressure is still moderately raised after unilateral nephrectomy
Renal dysplasia with obstruction	2	Male	Severe hypertension progressive until death
Polyarteritis nodosa	1	Male	Moderate hypertension; death in congestive cardiac failure
'Essential' hypertension	1	Male	A child with moderate hypertension; a unilateral nephrectomy failed to control the blood pressure; he is still under treatment five years later with anti-hypertensive drugs
Emotional hypertension and anorexia nervosa	1	Female	A 12-year-old girl with moderate hypertension treated with anti-hypertensive drugs for four years; she developed anorexia nervosa which was treated successfully four years after the onset of the hypertension; the blood pressure became normal and she became normotensive without drugs
A variety of unassociated conditions, cerebral cyanosis, sagittal sinus thrombosis, anaphylactoid purpura, post-tonsillectomy haemorrhage, idiopathic acrodynia	5	4 male 1 female	In all cases the hypertension was moderate and had become normal within four weeks

large vacuolated eosinophilic cells and their oval nuclei. There was less pleomorphism of these cells than in Case 1 and no mitotic figures were seen.

Measurements were taken of 100 of the large cells and their nuclei and an average figure obtained. Three other adrenal medullary sections from children of the same age as Case 2 were similarly measured. One patient in the control group was hypertensive (chronic nephritis), but the measurements obtained for this child were compatible with the two normotensive controls.

The figures obtained are listed in Table 2. They reveal an increase in size of cells and nuclei similar to that observed in Case 1.

Incidence of Hypertension

In the assessment of 20 cases of hypertension seen at the Royal Children's Hospital over the seven-year period (1952-1959) only those cases without nephritis and cardiovascular disease were included.

In Table 3, the term 'moderate' hypertension is used when the systolic pressure is below 180 mm. Hg and the diastolic below 120 mm. Hg. The term 'severe' hypertension has been reserved for pressures above these.

Discussion

Arising from the investigations of the cases in this paper, the following points will be discussed; the male preponderance and the incidence of the cases of medullary hyperplasia in the hypertensive children, the observations favouring adrenal medullary hyperplasia as a separate entity, the position of renal factors in hypertension and the possible sites of production of the pressor substance, the complexity of hypertension in man and the place of adrenalectomy in the management of malignant hypertension. The study of the hypertensive children (Table 3) reveals a male preponderance

of four to one; 16 of the 20 patients were boys and four were girls.

The examples of medullary hyperplasia form a clinical group the incidence of which in this analysis is comparable with that of the well-documented group of phaeochromocytoma.

The Group—Is it an Entity? The medullary cells of Cases 1 and 2 were indisputably hypertrophic. In Case 2 the medulla of the adrenals was the only pathological feature observed on autopsy which could account for the hypertension. No definite tumour tissue was demonstrated elsewhere after careful and extensive search.

Classification of S.W. (Table 2) is difficult because of lack of histological studies. All the clinical tests were negative and this case presents clinical features similar to Case 2, so perhaps the underlying cause of the hypertension was hyperplasia of the adrenal medulla. The persistent severe hypertension could have caused renal damage (Wilson and Byrom, 1939) and death in renal failure two years after the original investigations.

In the complex case (Case 1) it seems likely that the adrenal medullary hyperplasia was of primary importance as neither routine microscopy nor microdissection suggested any basic renal abnormality which could have predisposed to the development of pyelonephritis in this child (Ericsson and Ivemark, 1958; Bialestock, 1958). Kimmel (1942) examined an extensive series of children with pyelonephritis and found that only 10% showed a significant rise in blood pressure. On the other hand, experimental studies (Woods, 1958) have shown that hypertension *per se* can predispose to the development of pyelonephritis. Thus, in Case 1 the hypertension arising from the adrenal medullary hyperplasia could have been the primary cause of the renal damage.

These cases exhibit a pathological state of hypertrophy of the adrenal medulla. It seems reasonable to assume that the hypertrophy arises from increase in function. With the tests now in use pressor substances produced by these cells were not identified. It is postulated that medullary hyperplasia with its clinical effects on blood pressure should be regarded as a new group.

There has been of recent years a phase in management of hypertension which favoured excision of a small or abnormal kidney. Now that these patients have been scrutinized in the light of subsequent history, much doubt has been cast on this form of treatment.

Schwarz (1924) and Ask-Upmark (1929) had suggested on clinical grounds that the removal of one small kidney might benefit hypertensive children. The experiments of Goldblatt, Lynch, Hanzal and Sumerville (1934) gave stimulus to this notion and Butler (1937), Leadbetter and Burkland (1938) and Platt (1942) all reported on the beneficial effects of unilateral nephrectomy in hypertensive children.

However, Weiss and Chasis (1943), Smith (1948) and Peart (1959) are all in agreement that, in a large series, results of nephrectomy in management of hypertension have been disappointing.

As Smith (1948) has said, 'Had someone placed a clamp on the pancreatic artery before the days of Minkowski and obtained diabetes, he might well have been led to the theory, that all diabetes is due to pancreatic ischaemia or some other disturbance in the pancreatic circulation. This is, of course, not true; it is probably a very rare case in which the pancreatic circulation plays a part'. The same remarks may be applied to the Goldblatt experiment.

In Case 1 the vascular abnormality was similar to that in a Goldblatt experiment, yet removal of this kidney failed to lower the blood pressure. The remaining kidney was one with severe pyelonephritis. Observations from cases of pyelonephritis in childhood make this condition alone unlikely to be the main cause of hypertension. The hyperplasia of the adrenal medulla might have been the factor responsible for the hypertension and could have predisposed to the development of pyelonephritis.

Pressor material is undoubtedly produced by the kidney under some conditions. Goormaghtigh (1945), Dunihue (1941) and Demopoulos, Kaley and Zweifach (1960) have postulated that the site of production of this pressor material is the granules in the cells of the juxtaglomerular apparatus. Friedman and Kaplan (1943) and Des Prez (1948), on the other hand, maintain that the epithelium of the proximal tubule is the more important site of formation of pressor substance.

In Case 1 the stain for the juxtaglomerular cells of Goormaghtigh revealed that there was an increase in granularity of these cells in the left kidney and in those parts of the right kidney which were supplied by the normal calibre blood vessels. However, hypertrophic tubules in the same vascular distribution also contained similar blue granules. If the granules characterize cells which liberate the pressor substance then these observations indicate that in Case 1 both the juxtaglomerular bodies and the tubules might be involved in the formation of pressor substance.

The studies on the three cases, Case 1, Case 2 and S.W., make it unlikely that local renal factors were the only causes of the hypertension, so that

we have to look further. Hyperplasia of the adrenal medullary cells which was an outstanding feature of two of these patients is a likely primary cause.

Complexity of Hypertension. In man the mechanism of hypertension is probably extremely complex. There is little doubt that renal and adrenal factors can play a part in clinical hypertension. Wilson's (1953) experiments have indicated that the normal kidney can inactivate adrenal pressor substances. He has suggested that kidneys and adrenals form part of a homeostatic mechanism, which, through control of tissue electrolytes, maintains the arteriolar tone.

Peart's (1959) report on the variation in response to renal transplantation in two sets of identical twins illustrates the complexity of the situation in man. In one twin the blood pressure fell to normal as soon as the transplanted kidneys commenced to function; in the other twin the blood pressure did not fall until the diseased kidney had been removed. He concluded that the pressor substance was formed in the kidney in the second case but not in the first.

Pickering, Wright and Heptinstall (1952) in a small group of children with bilateral renal disease, with one kidney smaller than the other, failed to control the hypertension after nephrectomy of the smaller kidney. After subtotal adrenalectomy, however, the blood pressure could be kept under control and the children were growing and developing normally up to six years after operation.

Studies on the incidence of adrenal medullary changes in hypertension have been made from adult material. Drake *et al.* (1944) reported a high incidence of hyperplasia of adrenal medullary cells in hypertension, while Sommers (1959), with a much larger series, did not support Drake's observations. Sommers reported on the changes seen in adrenals of 97 hypertensive patients. In 80% of these the adrenals were histologically normal. Cortical adenomas and phaeochromocytomas are discussed. He makes no mention of simple hyperplasia of adrenal medullary cells. It seems likely that hyperplasia is a phenomenon exhibited by hypertensive children, that the condition is uncommon, and that it should be suspected when all clinical tests have proved unrewarding.

Hormonal factors in relation to hypertension may be still more complex than those of the adrenal and kidney components, as, in three cases described by Schroeder (1953), even after adrenalectomy, the blood pressure failed to fall to normal, and it has been suggested that other endocrine organs, e.g. pituitary, are probably disturbed in these cases.

Several authors (Thorn, Harrison, Merrill, Crisciello, Frawley and Finkenstaedt, 1952; Bowers, 1954; van T'Hoff, 1957) have reported encouraging results in the management of malignant hypertension with bilateral adrenalectomy.

If it can be shown by adrenal biopsy that the adrenal medulla is hyperplastic, as in the specific cases described in this paper, adrenalectomy and substitution therapy may be the logical form of treatment.

Conclusions

Clinical details are given from two children who died with severe hypertension. In both specimens hyperplasia of the adrenal medulla was found.

In one case medullary hyperplasia of the adrenal gland was the only lesion, whilst in the other pyelonephritis was present also.

Medullary hyperplasia should be considered as a disease entity for two reasons: (*a*) in one of the patients, this was the only lesion found at autopsy to account for the hypertension, and (*b*) because the hypertension persisted after excision of the ischaemic kidney in the second case.

There were two proven cases and one suspected case of medullary hyperplasia in a series of 20 patients exhibiting hypertension (excluding cardiovascular disease and glomerulonephritis).

In Case 1 the study of the nephrons by means of microdissection failed to reveal nephron abnormalities which might predispose to development of pyelonephritis. It could be that the hypertension of adrenal origin could have been the predisposing factor in the development of the pyelonephritis in this child.

Study of the juxtaglomerular apparatus of Goormaghtigh indicated that pressor substance is probably formed in both the juxtaglomerular bodies and in hypertrophic tubules.

I wish to thank the Senior Medical Staff of the Royal Children's Hospital, Melbourne, for access to case records, and Dr. A. L. Williams, Director of the Pathology Department, for help with the autopsy reports and criticism in the preparation of the paper.

References

Ask-Upmark, E. (1929). Über juvenile maligne Nephrosklerose und ihr Verhältnis zu Störungen in der Nierenentwicklung. *Acta path. microbiol. scand.*, **6**, 383.

Bialestock, D. (1958). Microdissection study of nephrons and cysts from an infant with pyelonephritis. *Aust. Ann. Med.*, **7**, 93.

Bowers, R. F. (1954). Bilateral adrenalectomy for severe hypertension. *J. Amer. med. Ass.*, **154**, 394.

Bowie, D. J. (1936). Method for staining pepsinogen granules in gastric glands. *Anat. Rec.*, **64**, 357.

Butler, A. M. (1937). Chronic pyelonephritis and arterial hypertension. *J. clin. Invest.*, **16**, 889.

Daeschner, C. W. and Dodge, W. F. (1959). B. Special problems in the therapy of hypertension. Treatment of hypertension in childhood with and without renal disease. In *Hypertension: The First Hahnemann Symposium on Hypertensive Disease*, ed. J. H. Moyer, p. 601. Saunders, Philadelphia.

Dempopoulos, H., Kaley, G. and Zweifach, B. W. (1960). The histologic distribution of renin in the kidneys of the rat and rabbit. *Amer. J. Path.*, **37**, 443.
Des Prez, J., Jr. (1948). The juxtaglomerular apparatus of the D hypertensive kidney. *Amer. J. clin. Path.*, **18**, 953.
rase, R. L., Hibbard, J. S. and Hellwig, C. A. (1944). The adrenal medulla in various diseases. A histophysiologic study. *Arch. Path.* (*Chicago*), 37, 351.
Dunihue, F. W. (1941). Effect of cellophane perinephritis on the granular cells of the juxtaglomerular apparatus. *Ibid.*, **32**, 211.
Ericsson, N. O. and Ivemark, B. I. (1958). Renal dysplasia and pyelonephritis in infants and children. Part I and II. *A.M.A. Arch. Path.*, **66**, 255, 264.
Friedman, M. and Kaplan, A. (1943). Studies concerning the site of renin formation in the kidney; IV. The renin content of the mammalian kidney following specific necrosis of proximal convoluted tubular epithelium. *J. exp. Med.*, **77**, 65.
Goldblatt, H., Lynch, J., Hanzal, R. F. and Sumerville, W. W. (1934). Studies on experimental hypertension. I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *Ibid.*, **59**, 347.
Goormaghtigh, N. (1939). Existence of an endocrine gland in the media of the renal arterioles. *Proc. Soc. exp. Biol.* (*N.Y.*), 42, 688.
—— (1945). Facts in favour of an endocrine function of the renal arterioles. *J. Path. Bact.*, **57**, 392.
Howard, John E., Berthrong, M., Gould, D. M. and Yendt, E. R. (1954). Hypertension resulting from unilateral renal vascular disease and its relief by nephrectomy. *Johns Hopk. Hosp. Bull.*, 94, 51.
Kimmel, G. C. (1942). Hypertension and pyelonephritis of children. *Amer. J. Dis. Child.*, **63**, 60.
Leadbetter, W. F. and Burkland, C. E. (1938). Hypertension in unilateral renal disease. *J. Urol.* (*Baltimore*), **39**, 611.
McCrory, W. W. and Nash, F. W. (1952). Hypertension in children: A review. *Amer. J. med. Sci.*, **223**, 671.
Oliver, J., MacDowell, M. and Tracy, A. (1951). The pathogenesis of acute renal failure associated with traumatic and toxic injury. Renal ischemia, nephrotoxic damage and the ischemuric episode. *J. clin. Invest.*, **30**, 1307.
Peart, W. S. (1959). Hypertension and the kidney. I. Clinical, pathological and functional disorders, especially in man. *Brit. med. J.*, **2**, 1353.
Pickering, G. W., Wright, A. D. and Heptinstall, R. H. (1952). The reversibility of malignant hypertension. *Lancet*, **2**, 952.
Pitcock, J. A. and Hartroft, P. M. (1958). The juxtaglomerular cells in man and their relationship to the level of plasma sodium and to the zona glomerulosa of the adrenal cortex. *Amer. J. Path.*, **34**, 863.
Platt, R. (1942). Unilateral renal disease and hypertension. *Proc. roy. Soc. Med.*, **35**, 317.
Ritchie, S. and Waugh, D. (1957). The pathology of Armanni-Ebstein diabetic nephropathy. *Amer. J. Path.*, **33**, 1035.
Schroeder, H. A. (1953). *Hypertensive Diseases—Causes and Control*, p. 327. Lea and Febiger, Philadelphia.
Schwarz, H. (1924). Kidney diseases in infants and children. II. Malignant hypertension nephritis; primary sclerotic kidney (schrumpfniere). *Amer. J. Dis. Child.*, **27**, 233.
Smith, H. W. (1948). Hypertension and urologic disease. *Amer. J. Med.*, **4**, 724.
Sommers, S. C. (1959). In *Hypertension: The First Hahnemann Symposium on Hypertensive Disease*, ed. J. H. Moyer, p. 22. Saunders, Philadelphia.
Thorn, G. W., Harrison, J. H., Merrill, J. P., Criscitiello, M. G., Frawley, T. F. and Finkenstaedt, J. T. (1952). Clinical studies on bilateral complete adrenalectomy in patients with severe hypertensive vascular disease. *Ann. intern. Med.*, **37**, 972.
van T'Hoff, W. (1957). Total adrenalectomy for malignant hypertension. *Quart. J. Med.*, **26**, 149.
Weiss, E. and Chasis, H. (1943). Failure of nephrectomy to influence hypertension in unilateral kidney disease. *J. Amer. med. Ass.*, **123**, 277.
Wilson, C. (1953). Renal factors in the production of hypertension, Part I and II. *Lancet*, **2**, 579, 632.
—— and Byrom, F. B. (1939). Renal changes in malignant hypertension—experimental evidence. *Ibid.*, **1**, 136.
Woods, J. W. (1958). Susceptibility of rats with hormonal hypertension to experimental pyelonephritis. *J. clin. Invest.*, **37**, 1686.

THE MYENTERIC PLEXUS IN INFANTILE HYPERTROPHIC PYLORIC STENOSIS

BY

J. R. RINTOUL and N. F. KIRKMAN

From the Department of Anatomy, University of St. Andrews, and Department of Anatomy, University of Manchester and Duchess of York Hospital for Babies, Manchester

(RECEIVED FOR PUBLICATION MARCH 29, 1961)

The aetiology of pyloric stenosis in infants is still uncertain. Since the early description of the condition by Blair (1717) various theories of pathogenesis have been formulated. It is now generally accepted that there is a defect in a gene. Carter and Powell (1954), by tracing the offspring of parents, one of whom had pyloric stenosis, showed that one son out of 10 and one daughter out of 50 born to such parents, would develop pyloric stenosis. This view is supported by the fact that the present incidence of three to four cases per 1,000 live births is much higher than the incidence recognized before 1900 (Cautley and Dent, 1903), which in turn may be attributable to the high survival rate of infants operated on for this condition (Wood and Smellie, 1951; Gross, 1953; Aird, 1957; Svenson, 1958).

Recent investigators have suggested that the condition may be the sequela to autonomic imbalance in the stomach (Cameron, 1925; Bendix and Necheles, 1947). Various aetiological theories have been advanced to explain this hypothesis. Some workers (Friesen, Boley and Miller, 1956; Taylor, 1959) believed that immaturity of the myenteric ganglion cells was the primary factor, while others (Herbst, 1934; Belding and Kernohan, 1953; Alarotu, 1956; Nielsen, 1956; Roberts, 1959) considered that degeneration of these neurons was responsible for the disease.

According to Friesen *et al.* (1956) the pyloric myenteric ganglia in cases of hypertrophic stenosis contain many undifferentiated cells. The presence of these cells suggested that final maturation of the ganglion cells, which normally occurs two to four weeks after birth, had been arrested or delayed. Roberts (1959), on the other hand, postulated that if this explanation were true, then one might expect an increased incidence of hypertrophic stenosis in premature infants.

Those claiming to have obtained microscopical evidence of degenerative changes in the myenteric ganglion cells differ somewhat in their descriptions of the signs of degeneration observed. Belding and Kernohan (1953) examined the stomachs of nine infants who had died from congenital pyloric stenosis and found that the majority of ganglion cells had undergone changes. The nuclear membrane was indistinct and the nucleolus appeared to be separated into two or three segments or to have disintegrated entirely. Numerous 'ghost cells' were found in all sections of the pylorus. These cells appeared merely as faint outlines of normal ganglion cells which had lost their normal staining reactions. Alarotu (1956) observed degenerative changes of varying severity in the pyloric myenteric ganglion cells. These changes appeared to occur with a certain regularity which enabled him to classify them into four types. Marked activity in the degenerating cells was manifested by increase in the size of the nucleolus and intense staining of the nuclear membrane. The nucleus was eccentric in position and frequently possessed two or more nucleoli. Severe degeneration was characterized by disintegration of the nucleus and ultimately by disappearance of the ganglion cells. Nielsen (1956) made similar observations from biopsy specimens obtained from the pyloric musculature of 15 infants submitted for surgical treatment of congenital pyloric stenosis. He reported severe degenerative changes in the intramuscular ganglion cells, the degree and type of degeneration varying from one specimen to another. In some specimens the cells showed evidence of chromatolysis; in others many atrophic cells were found. 'In the atrophic form the cells were excessively shrunken with a highly pyknotic nucleus.'

In addition to those changes in the ganglion cells a marked increase in the number of satellite cell nuclei and a pronounced proliferation of intercellular connective tissue was observed by those authors (Belding and Kernohan, 1953; Alarotu, 1956; Nielsen, 1956). Roberts (1959), however,

while he agreed with those workers that the ganglia were fewer in number and smaller in size in the abnormal pylorus, maintained that the cells were more tightly packed together than those in normal pyloruses.

Because of these differences of opinion we have reinvestigated the problem from the viewpoint of possible abnormality in the intrinsic innervation of the pylorus by examining the myenteric plexus in biopsy specimens of pyloric musculature from 38 infants with hypertrophic stenosis. The morphological appearance of the ganglion cells in those specimens was compared with that of the myenteric ganglion cells in normal pyloruses.

Material

Patients with congenital pyloric stenosis were treated by a wedge resection of pyloric muscle instead of a single pylorotomy as in Ramstedt's operation. Fig. 1 illustrates how the wedge biopsy was taken. The average size of the biopsy specimens was 10 × 4 × 3 mm.

Control material consisted of: (*a*) normal stomachs obtained from nine infants who had died from unrelated causes shortly after birth; (*b*) fresh tissue specimens of adult pylorus (six), duodenum (two), descending colon (two), secured at operation from patients who were treated surgically for gastric ulceration or carcinoma of the rectum.

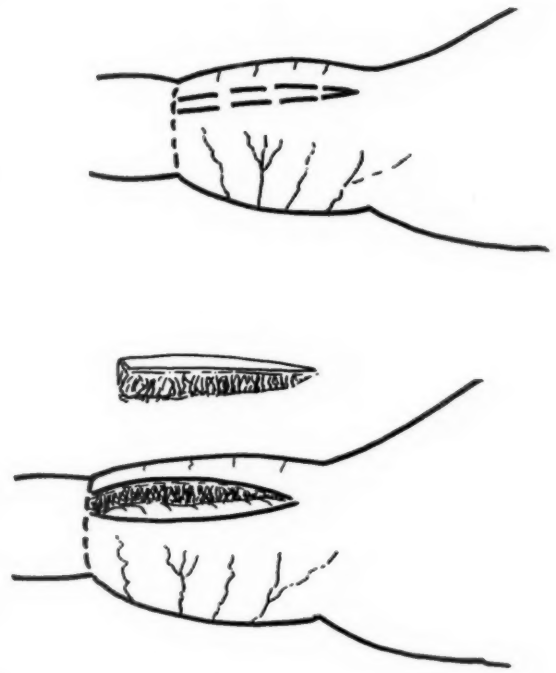


FIG. 1.—Diagram showing how the segment of pyloric musculature was obtained for examination.

Histological Methods

The biopsy and control material were placed in 20% (Analar) formalin immediately after excision.

Of the various neurohistological and routine staining methods used, the following gave the most satisfactory results: (A) A modified Bielschowsky-Gros silver impregnation technique; (B) haematoxylin (Delafield's) and eosin staining. Frozen sections 40μ thick were used in method (A) and serial paraffin sections in method (B). Before staining, the material to be submitted to haematoxylin and eosin staining, was either embedded in paraffin wax in the usual manner or prepared by the 'double embedding technique'. In the latter method the material, after dehydration, was immersed in 10% low viscosity nitrocellulose dissolved in methyl salicylate. When the material became transparent (usually after 24 to 48 hours) it was placed in benzene (two changes) to 'clear', transferred to paraffin baths and finally embedded in paraffin wax.

Observations

The examination of the biopsy and the control material was mainly concerned with a study of the morphological appearance of the myenteric ganglion cells and the structure of the nerve fibre tracts. Estimations of the total number of ganglia or of the number of ganglion cells present per unit area of muscle tissue were not undertaken since accurate measurements of the irregular wedge-shaped biopsy specimens were not possible. It is, however, well recognized that successful staining of all neural elements throughout an entire section is seldom, if ever, achieved where neurohistological staining methods are used.

In silver-stained preparations of the fresh control material (pylorus, duodenum, descending colon) two distinct ganglion cell types were recognized (Figs. 2, 3, 4, 5). One variety corresponded to the Type I cells described by Dogiel (1899). This cell type showed a marked affinity for silver, exhibiting heavy staining of the cell cytoplasm and cell processes and pale staining of the nucleus. The second cell type (Dogiel Type II) was found to be less argentophilic than Type I (Dogiel) cells and showed pale staining of the cytoplasm and heavier impregnation of the nucleus. The cell processes of the Type II cells usually remain unstained (Rintoul, 1959, 1960).

It has been observed previously (Rintoul, 1959) that the distribution of these different neuronal types appears to vary in different regions of the alimentary tract. This has been corroborated in the present study. Type II (Dogiel) cells were found to be uniformly distributed throughout the myenteric ganglia in both the control and biopsy material, whereas the more markedly argentophilic Type I cell appeared to be absent from tissue sections

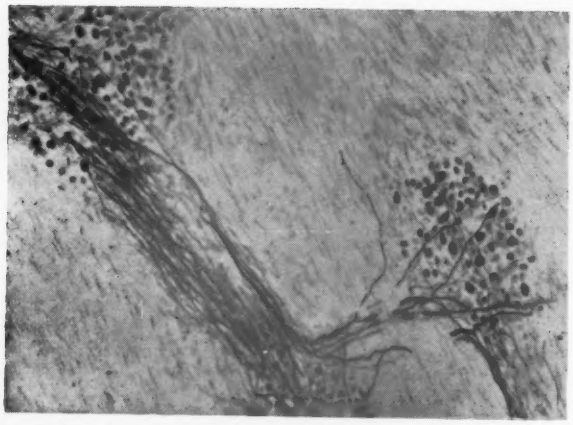


FIG. 2.—Portion of myenteric plexus from an autopsy specimen of normal infant pylorus. The cytoplasm of the ganglion cells (Type II) is faintly stained although the nuclei are heavily impregnated. (Modified Bielschowsky-Gros preparation. × 75.)

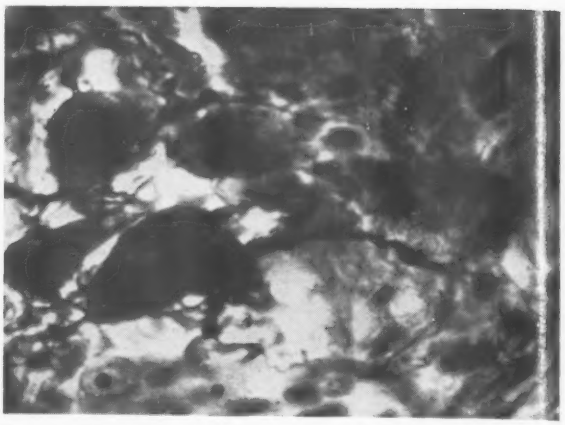


FIG. 3.—Myenteric ganglion in fresh control specimen of adult pylorus, showing Type I (Dogiel) neurons. (Modified Bielschowsky Gros preparation. × 400.)

FIG. 4.—Myenteric ganglion in adult duodenum, showing Types I and II (Dogiel) neurons (control specimen). (Modified Bielschowsky-Gros preparation. × 250.)

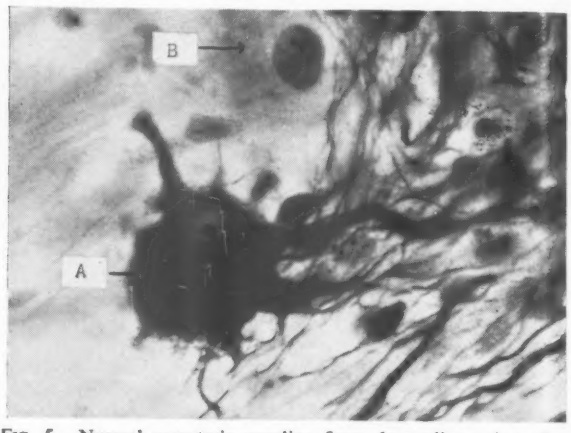


FIG. 5.—Normal myenteric ganglion from descending colon of an adult. Pointer (A) indicates a typical Type I (Dogiel) cell; pointer (B) indicates a Type II (Dogiel) cell. (Modified Bielschowsky-Gros preparation. × 400.)

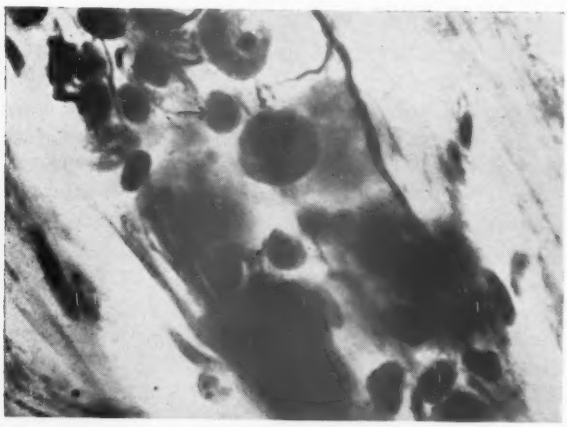


FIG. 6.—Myenteric ganglion in a biopsy specimen from an infant suffering from congenital pyloric stenosis. The ganglion cells which are of the Type II (Dogiel) variety show no obvious signs of degenerative change. Several satellite cell nuclei are visible, one of which is indicated by an arrow. (Modified Bielschowsky-Gros preparation. × 400.)

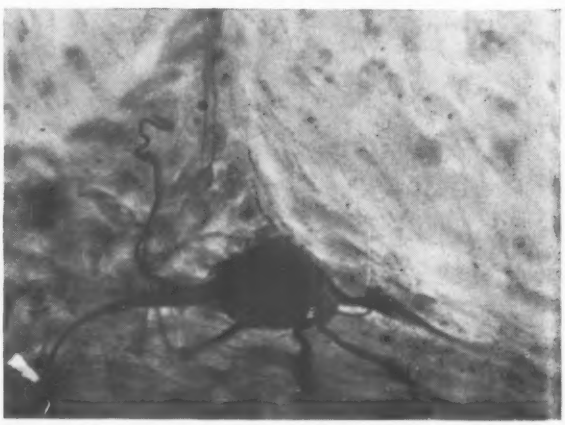


FIG. 7.—Pyloric myenteric ganglion from a biopsy specimen obtained at operation from an infant suffering from congenital pyloric stenosis. The argentophil Type I (Dogiel) cell shown is rarely found in such specimens. (Modified Bielschowsky-Gros preparation. × 400.)

of the biopsy material obtained from infants suffering from congenital pyloric stenosis.

There is, however, an exception to this observation. One section from several hundred silver-stained sections of biopsy specimens of pylorus (from infants suffering from hypertrophic stenosis) showed two type I neurons, one of which is illustrated in Fig. 7. In neither of these cells was the nucleus visible. The absence, or virtual absence, of Type I cells from the pyloric myenteric ganglia in the biopsy material suggests either that these cells were congenitally absent or that they had degenerated.

Careful scrutiny of the neurons (Type II) forming the pyloric myenteric ganglia in the biopsy specimens in silver-stained preparations failed to reveal the degenerative changes described by Belding and Kernohan (1953) and Nielsen (1956). Disappearance or fragmentation of the nucleoli or nuclear membranes, or pyknosis of the ganglion cells or their nuclei, such as those authors described, were not observed. Alarotu (1956) states that the presence of two or more nucleoli within the nuclei of the ganglion cells is indicative of increased physiological activity and that sustained stimulation of these ganglion cells ultimately leads to their degeneration. It is true that ganglion cells exhibiting two nucleoli may be seen in sections of biopsy specimens of the pyloric musculature (Fig. 6), but the more advanced signs of degeneration such as disintegration of the nuclei were not evident. Satisfactory staining of Type II neurons was not obtained in all the biopsy specimens and this, together with the absence of Type I cells might be interpreted as indicating that degeneration of ganglion cells had occurred. Nevertheless, comparison with the control material revealed no obvious reduction in the numbers of the neurons nor an increased glial proliferation within the ganglia in the biopsy specimens of pylorus from cases of congenital pyloric stenosis. Furthermore, the nerve fibres within the tracts of the plexus were also normal in appearance.

Those investigators who claimed to have observed degenerative changes in the pyloric myenteric ganglion cells in individuals suffering from hypertrophic stenosis employed routine histological staining methods, including cresyl violet, gallocyanine and haematoxylin and eosin. Using those methods microscopical appearances suggestive of degenerative change were frequently observed in both the biopsy and the control material. This appeared to be associated with the method of preparation of the specimen and was most evident in specimens prepared for sectioning by the usual procedure of embedding in paraffin wax. In those cases the ganglion cells were often shrunken and showed indistinct cells and nuclear membranes and pale staining of the cytoplasm. At times shadows of cells only were visible. These results are consistent with Nielsen's (1956) descriptions of ganglion cells undergoing chromatolytic degeneration. If, however, the double embedding technique (see 'Histological Methods') was used before the material was sectioned a different picture was obtained. The myenteric ganglion cells then have a more uniform appearance, showing distinct nuclear membranes and prominent nucleoli. Fig. 9 shows the typical appearance of the ganglion cells from a biopsy specimen prepared by the double embedding method and stained by haematoxylin and eosin. Evidence of autolytic change was observed only in some of the control material which had been obtained at autopsy and fixed several hours after death (Fig. 10). The microscopic picture of the myenteric ganglia in fresh control material (Figs. 8 and 11) was essentially similar in appearance to that seen in the biopsy material from cases of congenital pyloric stenosis (Fig. 9). Adequate staining of the ganglion cells was not, however, obtained in all of the specimens of the biopsy and control material examined. This defect in staining appeared to be more evident in preparations of infantile pylorus, derived from both the biopsy and control specimens, than in preparations of fresh control adult material. In the latter the ganglion cells were more clearly revealed by the stain (Figs. 8 and 11).

Discussion and Conclusions

Various theories have been advanced regarding the aetiology and pathogenesis of infantile hypertrophic pyloric stenosis. Current opinion suggests that the condition develops as a result of a defect in the intrinsic nerve supply to the pylorus. There are two opposing views: (i) that the ganglion cells are immature due to delayed or arrested development; and (ii) that the ganglion cells undergo degeneration as a result of abnormal parasympathetic (vagal) stimulation.

Friesen *et al.* (1956), who held the former view, examined the myenteric plexus in biopsy specimens of pylorus from 18 patients suffering from the disease. They found that the number of mature ganglion cells appeared to be considerably fewer in the biopsy material than in similar specimens of normal pyloruses, although the total number of ganglion cells per unit area was essentially the same in both. Those authors did not indicate, however, what

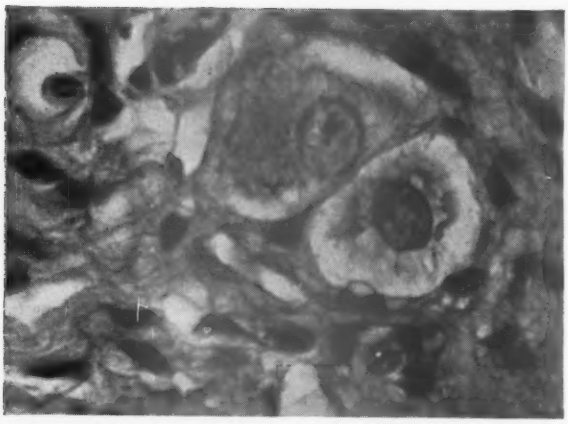


FIG. 8.—Pyloric myenteric ganglion from a biopsy specimen of normal adult pylorus. The considerable shrinkage of the cells which is usual in paraffin embedded specimens is evident. (Haematoxylin and eosin × 400.)

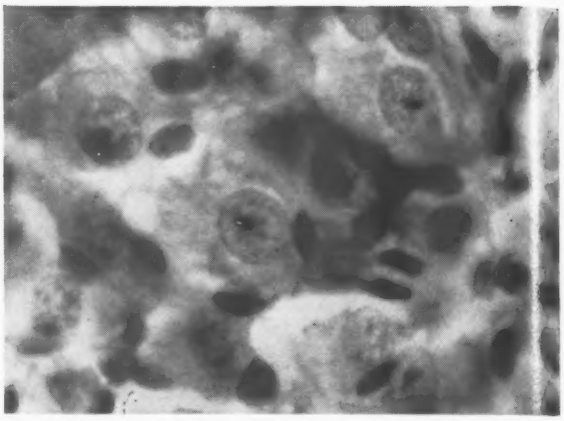


FIG. 9.—Myenteric ganglion of pylorus of an infant operated on for congenital pyloric stenosis. The ganglion cells appear normal and show well-defined nuclear membranes and nucleoli. Specimen prepared by 'double embedding' technique. (× 400.)

FIG. 10.—Myenteric ganglion from an infant pylorus obtained at autopsy (control specimen). Ganglion cells show evidence of autolytic change. (Haematoxylin and eosin × 400.)

FIG. 11.—Myenteric ganglion from descending colon of an adult (control specimen). Ganglion cells appear normal and show no evidence of shrinkage. Prepared by 'double embedding' technique. (Haematoxylin and eosin × 400.)

criteria they used to distinguish mature from immature neurons.

Other investigators (Belding and Kernohan, 1953; Alarotu, 1956; Nielsen, 1956) have disputed these findings. They believed that the total number of ganglion cells per unit area was considerably less than normal in the pyloric myenteric plexus of patients with congenital pyloric stenosis, and that this reduction was due to the disappearance of neurons which had undergone degeneration. Abnormal neurogenic impulses mediated by preganglionic vagal fibres were thought to be responsible for such degeneration. Belding and Kernohan (1953) and Alarotu (1956), considered that the microscopical appearance of these degenerating ganglion cells was identical to the histological picture obtained experimentally after prolonged stimulation of the vagus nerves. Moreover, in those cases where degeneration of the neurons had reached an advanced stage an increased proliferation of the intraganglionic glial tissue was usually evident (Nielsen, 1956).

In this investigation 38 biopsy specimens of pyloric muscle, obtained at operation from children with congenital hypertrophic stenosis, were examined histologically for evidence of immaturity or degeneration of the myenteric ganglion cells. The view that the ganglion cells were immature was tested by comparing the microscopical appearance of the cells present in the biopsy specimens with those of the control series which had been prepared for histological examination in an identical manner. The control specimens included material from the digestive tract of both infants and adults. Where

routine staining methods such as haematoxylin and eosin were used, it was observed that the ganglion cells were more difficult to stain in preparations of infant pylorus (from both biopsy and control material) than those in preparations of fresh adult control specimens. Since no such difference was noted in silver-stained preparations, we are unable to comment further on this observation.

Staining of the myenteric plexus by a silver impregnation technique was found to give more consistent results than those obtained by using routine laboratory staining methods. In sections prepared by the former method the myenteric ganglia were found to comprise several layers of closely packed cells with the minimum of supporting tissue. Two morphologically distinct ganglion cell types were recognized in tissue sections of the fresh control material. These cells types appeared to correspond to the Types I and II neurons described by Dogiel (1899). The Type I (Dogiel) cell was observed to be more markedly argyrophilic than the Type II (Dogiel) neuron. Examination of silver-stained preparations of the biopsy material showed that the argyrophilic Type I (Dogiel) cell was virtually absent from the pyloric myenteric ganglia in specimens from infants suffering from congenital pyloric stenosis, although no obvious reduction in the numbers of Type II (Dogiel) cells was noted. Whether the absence of the Type I cells is due to degeneration of these cells subsequent to excessive parasympathetic stimulation, or is attributable to some failure in their development is uncertain. It is noteworthy, however, that no evidence of disintegration and ultimate disappearance of neurons accompanied by replacement overgrowth of connective tissue was observed in those sections where adequate staining of the neurons was achieved.

Since previous workers have found that routine staining methods (including cresyl violet, gallocyanine and haematoxylin and eosin) were more satisfactory than neurohistological methods for revealing evidence of neuronal degeneration, preparations stained by these methods were also tried. It was found that where the specimens were prepared for histological examination by the usual method of paraffin wax embedding considerable shrinkage of the tissue occurred and indifferent staining of the pyloric myenteric ganglion cells frequently resulted. Shrinkage of the cell bodies and nuclei, together with pale staining of the cell cytoplasm and ill-defined cell boundaries gave a histological picture indistinguishable from that described by Nielsen (1956) as indicating early degenerative change in the myenteric ganglion cells. Since, however, similar appearances were obtained in the control specimens (Fig. 8), such evidence alone must be regarded as inconclusive and probably the result of inadequacies in the staining procedures employed.

Routine staining methods were found, however, to give results comparable to those obtained by the silver impregnation method when the tissue was first prepared for histological examination by the 'double embedding' technique. This method resulted in less shrinkage and distortion of tissue than simple paraffin wax embedding. Subsequent staining with haematoxylin and eosin was found to be more complete and uniform when the 'double embedding' method was used. Nevertheless, despite the improvements in staining obtained by this method, conclusive evidence either against the degeneration theory or in support of it was not secured because the ganglion cells were always more completely stained in specimens of adult than in specimens of infant pylorus. Certainly it is true that no advanced signs of neuronal degeneration, such as previous workers have described, were found. The possibility that early degenerative changes in the neurons are present, but have not been revealed by the staining procedures used, cannot be excluded.

Summary

Current opinion suggests that the primary factor in the aetiology of infantile hypertrophic stenosis is a defect in the pyloric myenteric plexus. One view holds that the ganglion cells are immature; another that the cells are degenerated.

Thirty-eight biopsy specimens of pyloric musculature from infants treated surgically for the condition were examined histologically and compared with similar sections from control material. It was found that there were present in normal pylorus two morphologically distinct ganglion cell types corresponding to (Dogiel) Types I and II neurons, but that (Dogiel) Type I neurons were virtually absent from the pylorus in congenital pyloric stenosis. Whether the absence of Type I cells is due to degeneration of these cells subsequent to excessive parasympathetic stimulation or to some failure in their development is uncertain.

No evidence of advanced neuronal degeneration in biopsy specimens of pylorus from infants suffering from congenital pyloric stenosis was found. Signs of nerve degeneration described by previous workers may be artefacts caused by imperfect methods of preparation of tissue for histological examination.

We wish to thank Professor G. A. G. Mitchell of the Anatomy Department of Manchester University for

his encouragement and advice during the period of this research and for the facilities which he provided in his Department.

Our thanks are also due to Dr. L. Stent of the Pathology Department of Withington Hospital, Manchester, for the provision of the autopsy specimens.

We also wish to acknowledge with gratitude the assistance given by Mr. L. Cooke in the preparation of the histological sections and that given by Mr. P. Howarth and Mr. J. Brown for the preparation of the photomicrographs.

References

Aird, I. (1957). *A Companion in Surgical Studies*, p. 1060. Livingstone, Edinburgh.

Alarotu, H. (1956). The histopathologic changes in the myenteric plexus of the pylorus in hypertrophic pyloric stenosis in infants (Pylorospasm). *Acta paediat.* (*Uppsala*), **45**, Suppl. 107.

Belding, H. H. and Kernohan, J. W. (1953). A morphologic study of the myenteric plexus and musculature of the pylorus with special reference to the changes in hypertrophic pyloric stenosis. *Surg. Gynec. Obstet.*, **97**, 322.

Bendix, R. M. and Necheles, H. (1947). Hypertrophic pyloric stenosis. A follow-up study. *J. Amer. med. Ass.*, **135**, 331.

Blair, P. (1717). An account of the dissection of a child. Communicated in a letter to Dr. Brook Taylor, R.S. Secr. *Phil. Trans. B*, **30**, 631.

Cameron, H. C. (1925). Some forms of vomiting in infancy. *Brit. med. J.*, **1**, 815.

Carter, C. O. and Powell, B. W. (1954). Two-generation pyloric stenosis. *Lancet*, **1**, 746.

Cautley, E. and Dent, C. T. (1903). Congenital hypertrophic stenosis of the pylorus and its treatment by pyloroplasty. *Med.-chir. Trans.*, **86**, 471.

Dogiel, A. S. (1899). Ueber den Bau der Ganglien in den Geflechten des Darmes und der Gallenblase des Menschen und der Säugethiere. *Arch. Anat. Physiol., Lpz., Anat. Abth.*, **61**, 130.

Friesen, S. R., Boley, J. O. and Miller, D. R. (1956). The myenteric plexus of the pylorus: its early normal development and its changes in hypertrophic pyloric stenosis. *Surgery*, **39**, 21.

Gross, R. E. (1953). *The Surgery of Infancy and Childhood.* Saunders, Philadelphia.

Herbst, C. (1934). Mikroskopische Untersuchungen der intramuralen Magennerven beim Pylorospasmus. *Z. Kinderheilk.*, **56**, 122.

Nielsen, O. S. (1956). Histological changes of the pyloric myenteric plexus in infantile pyloric stenosis. Studies on surgical biopsy specimens. *Acta paediat.* (*Uppsala*), **45**, 636.

Rintoul, J. R. (1959). The comparative morphology of the enteric neurons (Proc. Anat. Soc. Gt. Brit. and Ireland). *J. Anat.* (*Lond.*), **93**, 583.

—— (1960). The comparative morphology of the enteric nerve plexuses. M.D. Thesis, University of St. Andrews.

Roberts, P. A. Lane (1959). Pathology of infantile hypertrophic pyloric stenosis. *Proc. roy. Soc. Med.*, **52**, 1022.

Svenson, O. (1958). *Paediatric Surgery*. Appleton-Century-Crofts, New York.

Taylor, Selwyn (1959). Pyloric stenosis before and after Ramstedt. *Arch. Dis. Childh.*, **34**, 20.

Wood, E. C. and Smellie, J. M. (1951). Congenital hypertrophic pyloric stenosis. Review of 320 cases. *Lancet*, **2**, 3.

SEX-LINKED HYDROCEPHALUS

REPORT OF A FAMILY WITH 15 AFFECTED MEMBERS

BY

J. H. EDWARDS, R. M. NORMAN and J. M. ROBERTS

From the Medical Research Council, Population Genetics Research Unit, Oxford, and the Burden Neuropathological Laboratory, Frenchay Hospital, Bristol

(RECEIVED FOR PUBLICATION FEBRUARY 8, 1961)

Congenital hydrocephalus is a common cause of stillbirth and infant death [in Birmingham (Record and McKeown, 1950), Rhode Island (MacMahon, Pugh and Ingalls, 1953), and in Scotland (Edwards, 1958)], the incidence lying between one and two per thousand births, in each area the incidence being lower than that of either anencephalus or spina bifida.

When the heterogeneous assembly of cases so designated is analysed intact it seems clear that genetic syndromes related to recessive or sex-linked recessive inheritance are rare as the incidence in siblings of propositi is very low.

Penrose (1946) found no case in 84 sibs born after the propositus; Record and McKeown (1950) only one case in 61 sibs born after the propositus; and MacMahon *et al.* (1953) no case in 55 sibs born after propositus; the overall incidence in these three series is one case in 200 siblings. Further analysis of the Birmingham data (Record, 1959) showed no affected male sibling of 50 male propositi.

When grouped together the cases resulting in stillbirth show a marked increase in risk with primogeniture and with maternal age, and also some increase with reduced social class of the father (Edwards, 1958), showing that a substantial proportion of cases are related to various environmental agencies.

In 1949 Bickers and Adams described a family in which all of the three sons and four of the six brothers of a healthy woman died at birth with hydrocephalus, none of the three sisters or two daughters being affected (Fig. 1). An autopsy on one case showed evidence of aqueductal stenosis. Bickers and Adams commented that, although the numbers were too small to attach much weight to their observations, the pattern of inheritance was entirely consistent with a sex-linked recessive mechanism.

The purpose of this paper is to present a further case of hereditary hydrocephalus pathologically similar to that described by Bickers and Adams, and showing, on far larger numbers, a pattern of inheritance entirely consistent with a sex-linked recessive mechanism. That is to say the syndrome appears to be the result of an abnormal gene carried on an X chromosome, the morbid influence of which is completely eclipsed in the presence of another X chromosome lacking this genetic aberration.

The Propositus

A stillborn male child with hydrocephalus was delivered by one of us. Post-mortem examination (Dr. C. H. Wrigley) showed no abnormality outside the skull, and in view of the extraordinary family history, the brain was referred for detailed neuropathological investigation. We are most grateful to Dr. Wrigley for this.

Neuropathological Findings. The brain weighed 285 g. after fixation and dissection. The lateral ventricles were grossly dilated, the thalami widely separated and the floor of the third ventricle membranous. The corpus callosum and septum pellucidum could not be identified. Sections from the thinned-out part of the cortex showed that the total depth of the cerebral wall was approximately 3 mm., the reduction being at the expense of the white matter. The nerve cells were closely crowded together and the cortical lamination resembled that found in a 6-month foetus. The cerebellum was normally proportioned and the depth of its external granular layer appeared normal for a full-term infant. The fourth ventricle was not dilated. The choroid plexus

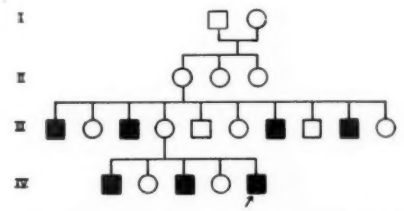


FIG. 1.—Family tree of cases described by Bickers and Adams (1949).

in the third ventricle was not atrophic. The brain was congested and the grey and white matter contained numerous haemorrhages. Its substance was extremely friable and easily disrupted and it was found necessary to dissect it while immersed in fixative. A block was removed which included the caudal extremity of the third ventricle and the rostral part of the fourth ventricle. This was embedded in celloidin and serially sectioned. Sections at 100μ intervals were stained for nerve cells by the carbol azure method and mounted for examination. Estimations of the cross-section of the aqueduct at certain points were made by projecting magnified images ($\times$40) on to graph paper, counting the squares and calculating the actual area of the lumen in square millimetres. These measurements were compared with those of the aqueducts in two stillborn non-hydrocephalic infants.

The Cerebral Aqueduct. In the control sections the normal variation in the calibre of the aqueduct was confirmed. Near its opening into the third ventricle below the posterior commissure the pars anterior measured 0·50 mm.^{2} (Fig. 2c). At the oral level of the trochlear nucleus a slight narrowing (superior constriction) occurred, the lumen measuring 0·44 mm.^{2} (Fig. 3b). This constriction was shortly followed by the ampulla which measured at its maximum 1·44 mm.^{2} (Fig. 4b). The inferior constriction, lying below the intercollicular sulcus, measured 0·62 mm.^{2} (Fig. 5b). The aqueduct then widened once more as it approached the fourth ventricle. The transverse shape of the lumen at these various sites corresponded closely with those illustrated by Gerlach (1858) and reproduced in Dorothy Russell's monograph (1949).

In the hydrocephalic brain the aqueduct was markedly reduced in calibre except at its caudal extremity (Fig. 6). The lumen was patent throughout and contained red blood cells evidently derived from a terminal intraventricular bleeding. The most rostral part of the pars anterior was reduced to a narrow slit too small to measure accurately by the method employed (Fig. 2a). Proceeding caudally a slight expansion (0·09 mm.^{2}) occurred (Fig. 2b) and this increased to 0·14 mm.^{2} at a level corresponding to the superior constriction in the normal brain (Fig. 3b). The largest transverse area of the ampulla measured 0·61 mm.^{2} (Fig. 4a) and at the site of the inferior constriction the area fell again to 0·14 mm.^{2} (Fig. 5a).

Irregularities of the ependymal layer were commonly seen and consisted of reduplication, focal heaping up of ependymal cells in the periaqueductal tissue or the presence of rosettes, the lumen of which did not communicate with the aqueduct. No forking, septum formation or periaqueductal gliosis was present. The tegmentum of the brain stem appeared unduly elongated dorso-ventrally, perhaps owing to obliquity of sectioning. The pes pontis was unduly small, the transverse fibres poorly represented, and there was no trace of descending corticospinal tracts.

Family Studies. The family was investigated in as much detail as possible. This was greatly complicated

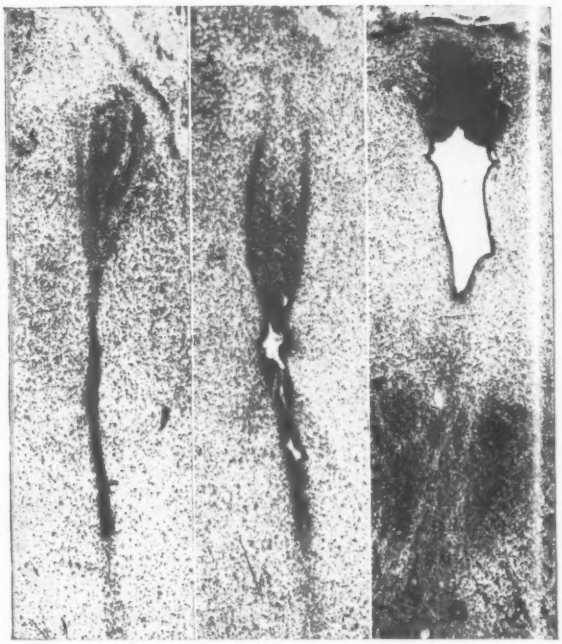


FIG. 2.—Pars anterior of aqueduct near opening into third ventricle. (*a*) and (*b*) from hydrocephalic brain showing the slit-like lumen. The subnucleus dorsalis is seen above. (*c*) normal brain at birth. (Carbol azure × 14.)

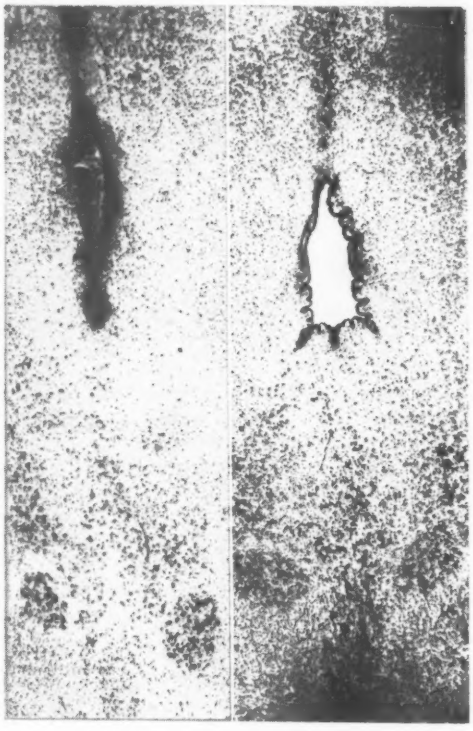


FIG. 3.—Level of superior constriction (*a*) hydrocephalic brain, (*b*) normal brain. Both sections at level of oral end of trochlear nucleus. (Carbol azure × 14.)

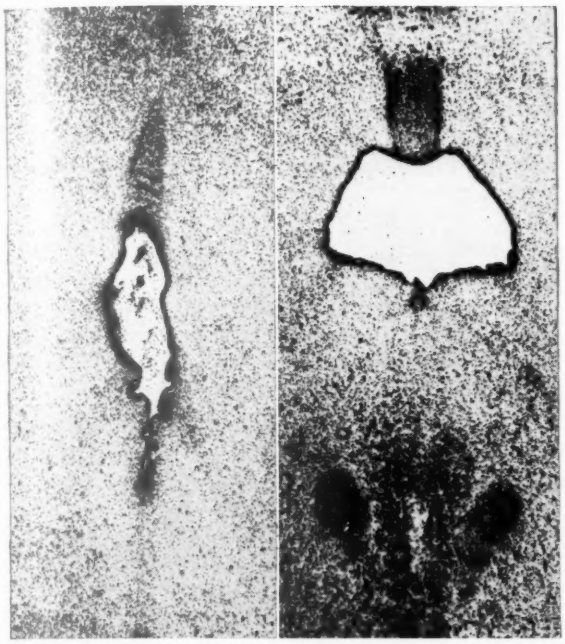


FIG. 4.—Ampulla at level of maximal dimensions. (*a*) hydrocephalic brain. (*b*) normal. (Carbol azure × 14.)

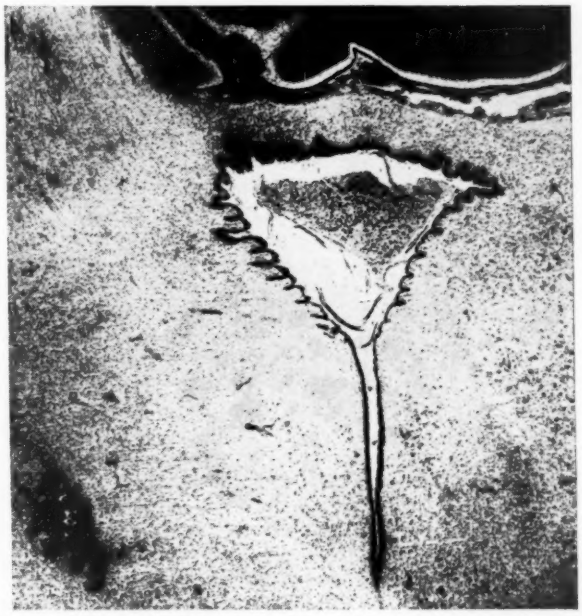


FIG. 6.—Hydrocephalic brain. Aqueduct near its entrance into the fourth ventricle. Note the large ependymal rosettes (bottom left). (Carbol azure × 14.)

by numerous moves as a result of the bombing and rebuilding of Southampton and by an unusual incidence of emigration. All available members of the family were visited by one of us and detailed histories taken. Other members living in Norway, South Africa, America and Canada provided further details by post. We are particularly indebted to Dr. Hertzberg and Professor H. J. Barrie of Toronto for details of further pregnancies of the mother of the propositus and for arranging to send the head of a further stillborn hydrocephalic (V. 14) to us. Unfortunately it did not arrive in an adequate condition for neuropathology.

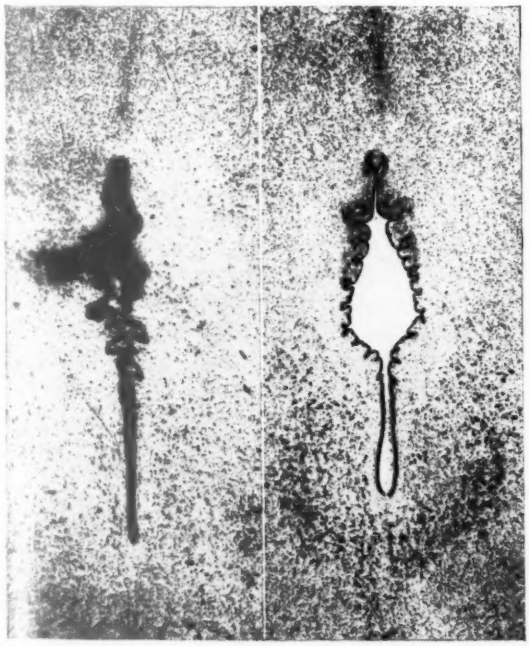


FIG. 5.—Pars posterior, level of inferior constriction. (*a*) hydrocephalic brain. Note the reduplication and displacement of the ependymal cells. (*b*) normal brain. (Carbol azure × 14.)

The family tree (Fig. 7 and the Table), derived from these sources, is entirely consistent and is believed to include all of the legitimate descendants of I. 1 and I. 2. It was not possible to obtain the maiden name of I. 1, who was thought by her descendants to have been born about 20 miles north of Southampton. An informal inquiry among paediatricians, pathologists and specialists in mental deficiency in the area failed to reveal any further cases. Allingham (1904) reported obstetric details relating to a stillborn hydrocephalic whose mother had given birth to three other stillborn hydrocephalics, had had five abortions and four normal children, in this area. The sex was not mentioned. A visit to the village of Whiteparish in which Allingham had his practice, and a discussion with the only practitioner in the village, were unrewarding.

Discussion

There is abundant evidence that severe narrowing of the cerebral aqueduct, whether caused by simple stenosis, forking, septum formation or pressure by a tumour, is usually associated with internal hydrocephalus. Yet the critical level in the reduction in

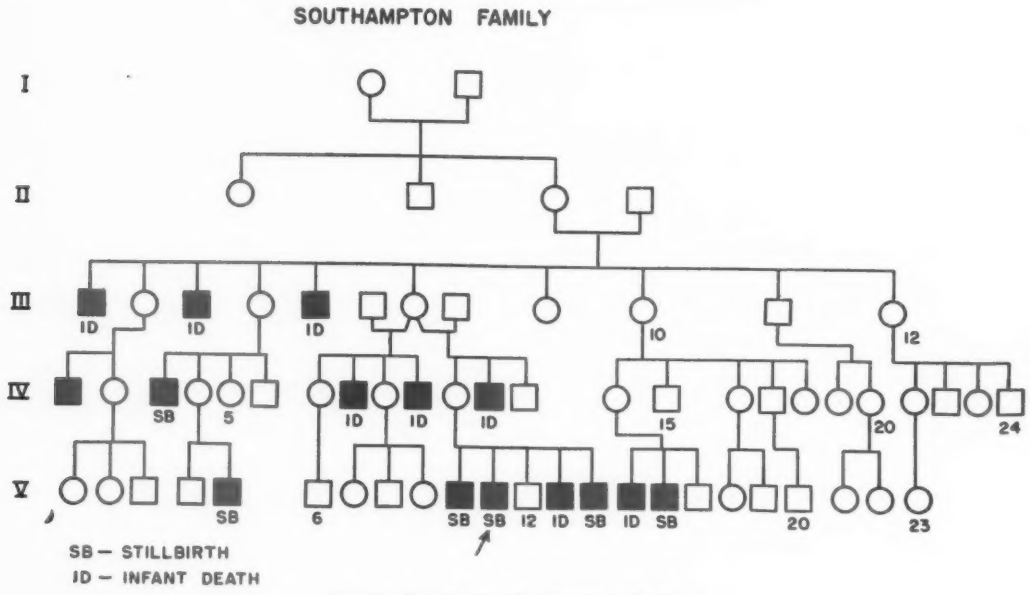


FIG. 7.—Family tree: Southampton family.

calibre of the aqueduct below which hydrocephalus is to be expected is far from established. The measurements made by Woollam and Millen (1953) on 14 normal adult aqueducts show surprising variations, the superior constriction varying from 0·2 mm.^{2} to 1·8 mm.^{2}, the ampulla from 0·8 mm.^{2} to 2·9 mm.^{2} and the inferior constriction from 0·4 mm.^{2} to 1·5 mm.^{2} It follows from these observations that stenosis of the aqueduct cannot plausibly be regarded as the cause of hydrocephalus unless the cross-section at the point of maximal constriction is less than 0·2 mm.^{2}.

TABLE

Family	Remarks
I 1, 2	Born about 1850, probably in Hampshire
II 1	Died childless in 1921, age 53
III 1	Died age 2; hydrocephalic
III 3	Died age 2; hydrocephalic
III 5	Died age 1; hydrocephalic
IV 1	Mental defective with gross hydrocephalus Unable to walk; held thumbs opposed across palms; died in 1943 age 18; no record of autopsy
IV 3	Stillborn; hydrocephalic
IV 8	Died age 8 months; hydrocephalic
IV 10	Died a few weeks after birth; hydrocephalic
IV 12	Died a few days after birth; hydrocephalic
IV 13	Premature birth following accident; stillborn Said to be completely normal but no records available
IV 18	Infant death from tuberculous meningitis while father was being nursed at home
V 5	Stillborn; hydrocephalic
V 10	Stillborn; hydrocephalic
V 11	Propositus; stillborn; hydrocephalic
V 12	Normal boy, age 4 (report from family doctor in Canada)
V 13	Died age 2 days; hydrocephalic
V 14	Stillborn; hydrocephalic
V 15	Stillborn; thought to be hydrocephalic by mother; hospital notes lost
V 16	Died a few days after birth; hydrocephalic

In the present case this requirement is fully met, since the cross-sections of both the superior and inferior constrictions (0·14 mm.^{2}) were much below Woollam and Millen's smallest normal figure. The most anterior part of the aqueduct was even narrower and was, indeed, too small for precise measurement by the method used, but the neighbouring tissue had been damaged by haemorrhage and it is conceivable, though unlikely, that lateral compression from oedema might have been partly responsible for the slit-like deformity of the lumen. However this may be, it is evident that the markedly subnormal dimensions of the whole aqueduct and the anomalous arrangement of the ependyma throughout much of its course are features more consistent with an early malformation than with the action of mechanical factors influencing the shape of a previously developed aqueduct.

These findings correspond closely to those recorded by Bickers and Adams (1949) in the only other published example of this inherited type of aqueductal stenosis. In their case also the stenosis was of simple type, that is, there was no periaqueductal gliosis and no forking of the channel. The maximal constriction also occurred anterior to the ampulla and measurements at this site taken from their illustration 2A give a cross-sectional area of 0·12 mm.^{2}, a figure of the same order as was found in our case.

The case described above, and the very extensive

and morbid family history appears to confirm fully the somewhat cautious claims of Bickers and Adams. The similarity in neuropathological findings and familial transmission are incontrovertible evidence of a variety of hydrocephalus resulting from aqueductal stenosis and transmitted as a sex-linked recessive. Structural congenital malformations due to single-gene effects are very rare in man and we are not aware of any well-established disorder in man in which an isolated and specific structural abnormality can be related to either recessive or sex-linked recessive transmission. A somewhat similar disorder, affecting a different part of the ventricular system and transmitted as an autosomal recessive, has been described in the mouse (for discussion and bibliography see Grüneberg, 1952).

Summary

A case of congenital hydrocephalus presenting in a family in which many males had previously been affected showed, on autopsy, a primary stenosis of the aqueduct of Sylvius. The pattern of inheritance was entirely consistent with recessive sex-linkage. The case appears very similar to that described by Bickers and Adams both in its morbid anatomy and its mechanism of transmission.

References

Allingham, W. (1904). Spinal catheterisation in a case of obstructed labour from congenital hydrocephalus. *Lancet*, **2**, 1566.

Bickers, D. S. and Adams, R. D. (1949). Hereditary stenosis of the aqueduct of Sylvius as a cause of congenital hydrocephalus. *Brain*, **72**, 246.

Edwards, J. H. (1958). Congenital malformations of the central nervous system in Scotland. *Brit. J. prev. soc. Med.*, **12**, 115.

Gerlach, J. (1858). *Mikroskopische Studien aus dem Gebiete der menschlichen Morphologie*. Enke, Erlangen.

Grüneberg, H. (1952). *Genetics of the Mouse*. Nijhoff. 1956 M.R.C. Memorandum No. 33.

MacMahon, B., Pugh, T. F. and Ingalls, T. H. (1953). Anencephalus, spina bifida, and hydrocephalus: Incidence related to sex, race, and season of birth, and incidence in siblings. *Brit. J. prev. soc. Med.*, **7**, 211.

Penrose, L. S. (1946). Familial data on 144 cases of anencephaly, spina bifida and congenital hydrocephaly. *Ann. Eugen. (Lond.)*, **13**, 73.

Record, R. G. (1959). Personal communication.

—— and McKeown, T. (1950). Congenital malformations of the central nervous system. II: Maternal reproductive history and familial incidence. *Brit. J. prev. soc. Med.*, **4**, 26.

Russell, Dorothy S. (1949). Observations on the pathology of hydrocephalus. *Spec. Rep. Ser. Med. Res. Coun.*, No. 265. H.M.S.O., London.

Woollam, D. H. M. and Millen, J. W. (1953). Anatomical considerations in the pathology of stenosis of the cerebral aqueduct. *Brain*, **76**, 104.

THE SYNDROME OF SEX-LINKED HYDROCEPHALUS

BY

J. H. EDWARDS*

From the Medical Research Council, Population Genetics Research Unit, Oxford

(RECEIVED FOR PUBLICATION MARCH 21, 1961)

Bickers and Adams (1949) and Edwards, Norman and Roberts (1961) have presented detailed neuropathological examinations on two cases of hydrocephalus secondary to aqueductal stenosis in families with many hydrocephalic males. These, taken together, provide incontrovertible evidence of a specific syndrome with sex-linked recessive inheritance. In this paper further families are described in which the same disorder appears to be manifest, although the basic observation of the neuropathology has not been made.

HISTORICAL

Borle (1953) has reviewed the reports of familial hydrocephalus; Gellman (1959) has reviewed reports of hydrocephalic twins, and Bickers and Adams have reviewed reports of aqueductal stenosis. Both Borle, and Bickers and Adams give detailed summaries. Although various familial cases, and some cases in which aqueductal stenosis was present, might plausibly be interpreted as exemplifying this variety of sex-linked hydrocephalus, no report previous to that of Bickers and Adams gives both familial and pathological data in adequate detail to define an entity.

Recent reports which are strongly suggestive of sex-linked hydrocephalus include Perez and Linger's (1947) report on a sibship with three affected stillborn boys, one with a bifid scrotum, and two normal girls. Bamatter (1949) quoted the case of a woman with two hydrocephalic boys and three normal girls. Zimmer (1952) reported two sisters of whom one had two stillborn hydrocephalic males and the other one stillborn hydrocephalic male, and gave brief histological details, referring to the increased vasculature and gliosis on the dorsal side of the mid-brain and hind-brain. No mention was made of the aqueduct. Borle (1953) reported three hydrocephalic brothers, two of whom were identical twins, the only children of healthy parents. The eldest, age 8, showed no abnormalities apart from a slight enlargement of the head (3·8 cm. above average) and lack of concentration. His twin brothers, age 5, were normal at birth, hydrocephalus developing insidiously and being apparent only after the first year. Walking started at the age of 2, speech at the age of 4. Both developed epilepsy at 8 months, an unusual complication of hydrocephalus. The family exemplifies some of the difficulties of applying any of the theoretical models of ascertainment, the diagnosis of hydrocephalus in the first case being made only after consideration of similarities to the other two. Gellman (1959) referred to identical twin boys, age 5, with hydrocephalus and mental deficiency. Air studies showed moderate symmetrical ventricular dilatation. The photographs are strikingly similar to those of the two brothers (Figs. 1 to 6) showing a large oblong head, thin legs, and apparent inability to plantigrade with the knees straight; one shows opposition of the thumbs.

CASE REPORTS

Family I: The Bromyard Family

The presenting cases, Glynn (Figs. 1, 2, 3; IV 15 in Fig. 7) and Martin (Figs. 4, 5, 6; IV 16 in Fig. 7) were referred simultaneously to Dr. Clifford Parsons by Dr. M. J. Peto with the comment that the family suffered from hereditary hydrocephalus affecting only the males.

Glynn, age 9. (The Children's Hospital, Birmingham. EB/137960.) Caesarian delivery after radiological diagnosis of hydrocephalus during prolonged labour. Birth weight 7 lb. 6 oz. At birth both thumbs were turned in across the palms. Development was slow up to the age of 3, after which there has been little advance, and he has persisted with the mental attributes of a 2-year-old. He is a happy and active child. Intelligence testing suggested rather more advanced development with a mental age of 2·9 years (I.Q. 30), but he was not fully continent and knew few words.

Physical examination. No abnormality was apparent apart from the head, hands and stance. The head was irregularly enlarged, approximately 2·5 cm. above the average circumference for that age, and unusually oblong.

* Present address: The Children's Hospital of Philadelphia.

FIG. 1.—Glynn: face.

FIG. 2.—Glynn: stance.

FIG. 4.—Martin: face.

FIG. 5.—Martin: stance.

FIG. 3.—Glynn: hands.

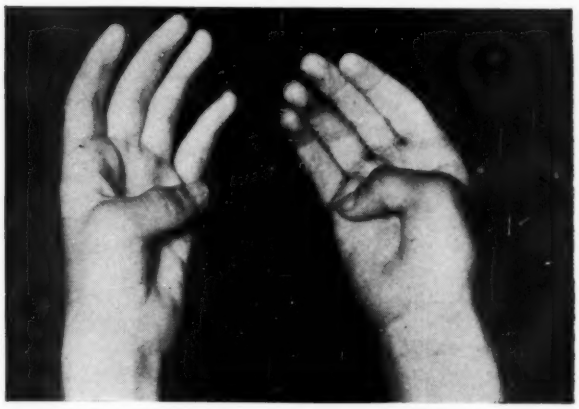


FIG. 6.—Martin: hands.

The face appeared somewhat coarse. The eyes were rather deep set. White flakes were present on the irides: these did not show the typical horseshoe-shaped fibrous strands seen in mongolism and the irides were otherwise well developed. The hands and stance were as shown. The reflexes were not increased in the arms, which showed full power and no increased tone. The legs showed marked spasticity with loss of power and very brisk reflexes. The plantar responses were extensor.

Investigations showed urine with amino acid and sugar chromatography normal, and concentration and dilution tests normal; blood with electrolytes and proteins normal; urea 31 mg./100 ml.

Radiograph showed large cranial vault, but no evidence of cause of hydrocephalus.

An electroencephalogram revealed diffuse symmetrical abnormalities; no epileptic phenomena were present.

Martin, age 8. (The Children's Hospital, Birmingham. EB/137961.) Full-term normal delivery; birth weight 6 lb. 5 oz. The head did not appear large at birth and the parents had not noticed any subsequent enlargements. The hands were like Glynn's with in-turning of the thumb apparently uninfluenced by operative procedures. He sat up at 6 months, walked at 12 months, but has never talked properly. Speech appeared slurred but there were no other cerebellar signs. Progress seemed to slow markedly at the age of about 1 year; at the age of 8 he had a mental age of about 2 years and was somewhat more retarded than his brother.

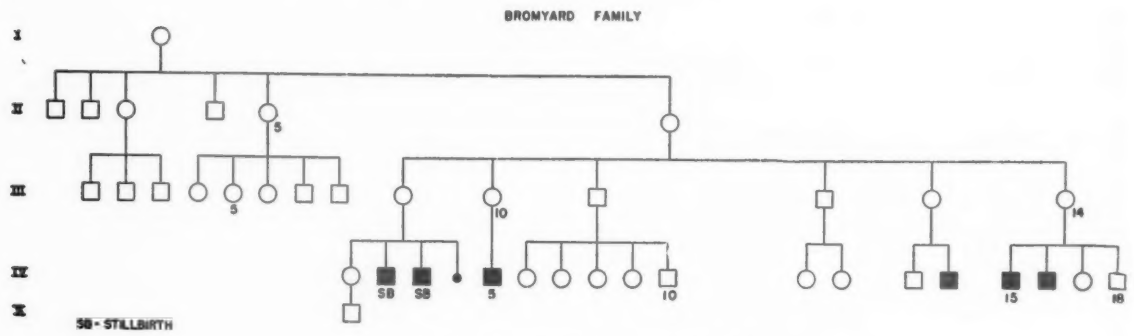


FIG. 7.—Family I: The Bromyard family.

Physical findings. These were identical to those described above. Apart from a slight difference in size these boys could easily be mistaken for identical twins.

Investigations on the urine revealed amino acid and sugar chromatography normal, and concentration and dilution test normal; blood, electrolytes and proteins were normal; urea 49 mg./100 ml.

A radiograph showed a large cranial vault with a long type of skull, slightly asymmetrical with probably premature closure of the sagittal sinus.

The hands showed short thumbs and first metacarpals.

An electroencephalogram indicated diffuse symmetrical abnormality, but no epileptic phenomena.

Family History. Through the kindness of Dr. Clifford Parsons and Dr. M. J. Peto, the family was visited. All living affected members, the mothers of all cases, and their grandmother were interviewed and given a detailed neurological examination including ophthalmoscopy. The pedigree (Fig. 7) shows six cases among the male children of four sisters. The grandmother (II 6) whose ancestry is from South Wales, must be assumed heterozygous for the defective gene: there is no evidence of any prior affected member and she has three normal brothers (II 1, 2, 4) and two sisters (II 3, 5) with three and two normal sons respectively.

IV. 1. Normal girl with normal son (V 1) age 6 months.

IV. 2. Induced delivery with perforation after intrauterine death. Hydrocephalus obvious (personal report from practitioner). Weight 12 lb.

IV. 3. Delivered dead after induction; hydrocephalic; weight 12 lb.

IV. 4. Spontaneous abortion at third month.

IV. 5. *Colin, age* 18. Normal delivery, 7½ lb. Normal infancy until head started enlarging at about 2 years of age. Head now long, irregular with slight bi-temporal bulges and a rather flat top; circumference 57 cm. Squint with the left eye turning in, which was said to have developed before enlargement of the head. Mental age about 3 years.

EXAMINATION. Cranial nerves and eyes were normal, apart from squint. Generalized weakness and poor co-ordination of arms, with normal or slightly increased tone and reflexes. Thumb is held across palm; structure confused by various orthopaedic procedures designed to correct this. Severe spasticity of legs with wasting, but basic disturbance confused by numerous operations; moderately brisk knee and ankle jerks; plantar responses definitely flexor.

IV. 14. *Michael, age* 12. Normal at birth. Sat at the age of 1 year and then made very little progress until starting speech at the age of 2 years. Intelligence at about 4-year-old level. Can speak well and ride a tricycle.

EXAMINATION. A healthy child with a slightly large head (53 cm.). Thumbs rather short and conical and tend to be held across palm. Arm reflexes normal. Unable to plantigrade due to contracture of calf muscles; tone greatly increased, but power good; knee jerks very brisk; ankle jerks normal; plantar responses extensor.

IV. 15. Glynn—see above.

IV. 16. Martin—see above.

IV. 17. Normal girl.

IV. 18. Normal boy, age 1. Hands, fontanelles and mental development normal for age.

Family II: The Thetford Family

Maurice. This case, which is probably sporadic (Maurice, IV 5; Fig. 8) is number 86 in Penrose's series of malformations of the nervous system where it is described as a case of hydrocephalus with flexion deformity of the thumbs (Penrose, 1946). (I am grateful to Professor Penrose for giving me a copy of his original notes and permitting me to visit the patient.) When seen in 1958 he was a large robust mentally deficient man, living at home as the only child of elderly parents with a local ancestry.

At birth, when his mother was 38, he appeared normal (weight 6 lb. 2 oz.), except that the thumbs were held in flexion across the palms. For the first year mental development was normal and speech started at 12 months, although physical development was slow and he still could not sit up unaided. After 12 months there was very slow progress, sitting unsupported at 3 years and walking at 5. His head was noticed to be large at 1 year, and continued enlarging until he was 5. Since then he

has made little progress and now has a mental age of about 3 years. He is continent, can dress, goes out alone, and is said to be able to identify all the local cars and buses by sound.

EXAMINATION. He had a fairly large irregular head, the enlargement being largely antero-posterior with a high occiput; circumference 60 cm. The face was asymmetrical, the left eye being sunken and below the right. The mouth and teeth appeared normal, apart from an unusually small right upper lateral incisor. The hands were normal, but he had rather small, probably atrophic, thumbs which were held almost permanently within the palm, but which could be extended and abducted either actively or passively without difficulty. His gait was grossly disturbed due mainly to inability to plantigrade. Ophthalmoscopy normal; colour vision normal. Cranial nerves normal. Tone, power and reflexes normal in arms. He is left-handed, has no cerebellar signs. (Although cerebellar signs were looked for in all patients and found in none, only in this patient was there sufficient co-operation to allow a reliable opinion on the absence of minimal signs.) Legs were distorted by contracture and wasting of the calf muscles, power probably slightly reduced; tone increased; knee jerks symmetrically increased; ankle jerks normal but in view of the small volume of calf muscle this probably represented abnormal excitability. Plantar responses extensor.

Family History. This was essentially negative. The mother of the case, III 5, was an intelligent woman, well informed about her family. Her eldest sib, III 1, died shortly after birth; she knows of no details except that there was no obvious cause and is uncertain of the sex. Another sib, a boy, III 2, died between the ages of 1 and 2 and is said to have been a normal child without abnormality of development, head size or hands. As these deaths were discussed in the family in relation to Maurice, this negative evidence appears reliable. Her mother's four sisters and two brothers were all healthy and all had two, three or four normal children.

In spite of the absence of both familial and pathological evidence the consistency of the complex of signs leads me to regard this case as a very likely example of sex-linked hydrocephalus. The high maternal age is possibly not fortuitous.

Family III: The Northampton Family

This pedigree (Fig. 9) was brought to my notice by Dr. Christopher Ounsted as a family exhibiting mental deficiency segregating as a sex-linked recessive with an unusually large proportion of affected males. I am most grateful to him and to Dr. I. H. Gosset, to whom the family is also well known, for their help. As usual, there cannot be said to be a propositus and the cases will be described in order of seniority starting with the larger sibship.

IV. 3. Alfred, age 17. Normal birth. He was slow in sitting and talking and has a mental age of about 2½ years. He has had three fits; is abnormally active and restless with a very short attention span. His head is oblong and irregular, 74 cm. in circumference; face asymmetrical with left eye raised. Arms show normal reflexes and normal power and tone. Right thumb is held opposed across palm. There is marked spasticity of legs with brisk jerks, loss of power, but no wasting. He cannot plantigrade, and plantar responses are definitely flexor. Radiograph of skull at the age of 3 suggested hydrocephalus.

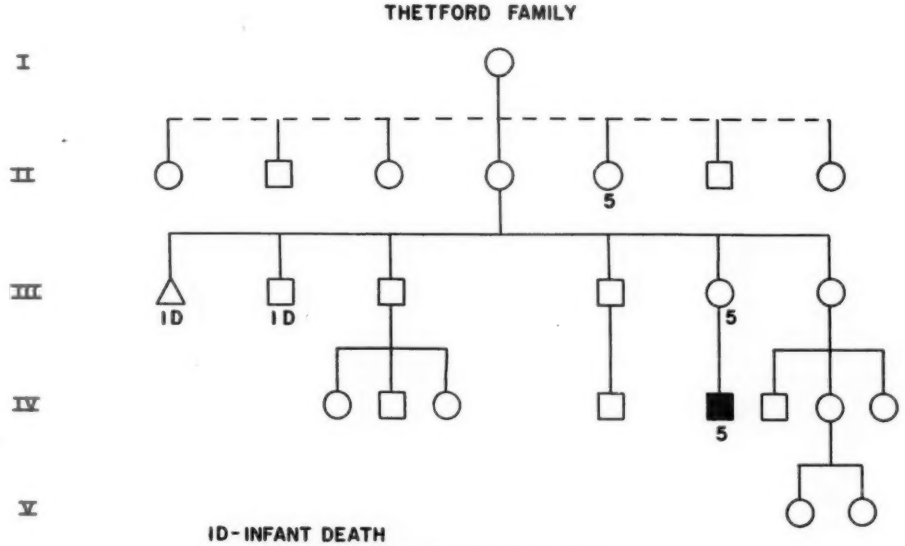


FIG. 8.—Family II: The Thetford family.

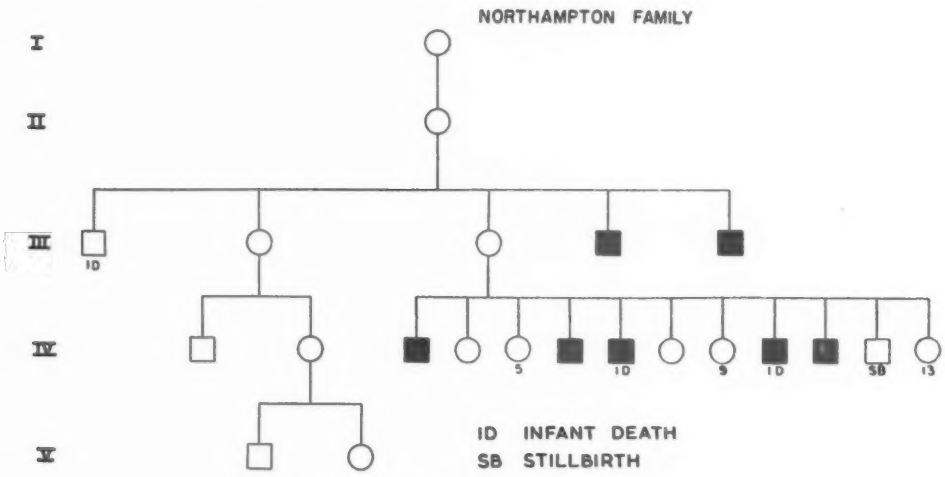


FIG. 9.—Family III: The Northampton family.

IV. 4. Normal girl.

IV. 5. Normal girl.

IV. 6. Aubrey, age 13. Appearance similar to IV. 3. Head is long and irregular. Face asymmetrical with right eye raised. Skull circumference is 53 cm. Mental age is about 3 years. Hands are normal apart from slightly small terminal phalanges to thumb. No neuromuscular abnormality apart from slightly brisk leg reflexes and abnormal tenseness of soleus; no ankle clonus; plantar responses flexor; can plantigrade foot.

IV. 7. Allan. Died age 4 months. During life showed obvious asymmetry of skull and was always sickly and too weak to feed properly. No autopsy was carried out.

IV. 8. Normal girl.

IV. 9. Premature baby girl, who died shortly after delivery. No abnormality noted.

IV. 10. Boy, died age 9 weeks. Clinical diagnosis on admission to hospital hydrocephalus and dehydration. At autopsy no abnormalities were found. The slides of the mid-brain did not include the aqueduct. In spite of the absence of pathological evidence it seems unwise to ignore the clinical diagnosis, and, as with the previous case, the balance of evidence appears to favour hydrocephalus.

IV. 11. Andrew, age 5. Face asymmetrical, skull circumference 53 cm. Mental age about 2½ years. No abnormalities on examination apart from rather small thumbs and a definitely abnormal increase of leg reflexes and tension of soleus. Plantar responses flexor. Recently had repair of squint.

IV. 12. Stillborn boy; no adequate history from mother; hospital notes lost.

IV. 13. Normal girl.

II. 1. Died five years ago; came from nearby town and was an only child.

III. 1. Died of meningitis between 2 and 3 years of age; details unknown.

III. 2. Not interviewed, but well known to III 3. Reports on the normality of her son (IV 1) and her daughter's son (V 1) appear reliable.

III. 3. Normal woman age 41 with no abnormal neurological signs apart from low intelligence.

III. 4. George, age 38. Institutionalized mentally defective man. A healthy, cheerful imbecile who can just dress and feed himself. Head rather long and irregular. Face asymmetrical with left eye higher than right. 'Prize-fighter's facies.' Thumbs show tendency to turn in. Terminal phalanges very small. Calf muscles contracted and feet clawed. Fundi normal. Power, tone and reflexes normal in arms. Legs spastic with slight loss of power and very brisk jerks. Plantar responses equivocal. Abnormal patchy pigmentation of skin.

III. 5. Sydney, age 32. Facies and intellect similar to above. Head long and irregular, 59·5 cm. in circumference. Hands probably normal; arms normal. Legs spastic with very brisk jerks, but with no contractures or wasting. Plantar responses unequivocally flexor.

The low intelligence of the parents of this large family, the death of the grandparents, the confusion generated among themselves by giving all their children similar names, and the mildness of manifestation, make this family the least adequately studied. The three eldest cases are, however, fairly typical, and the family was identified by observing one of these, Alfred, while passing their house.

Family IV: The Southampton Family

This family has been described in detail in the previous paper (Edwards *et al.*, 1961). Peter (IV 1), the only survivor of infancy of the 15 affected cases, died at the age of 18. He was a low grade mental defective with a very large head which he could only carry with difficulty. He could just walk and talk, was liable to violent tempers, and had the curious habit of holding his thumb within

TABLE 1
SEX-LINKED HYDROCEPHALUS

Area	Affected	Stillbirths	Infant Deaths	Late Deaths	Survivors
Present series	29	8	10	1	10
I. Bromyard	6	2	0	0	4
II. Thetford	1	0	0	0	1
III. Northampton	7	0	2	0	5
IV. Southampton	15	6	8	1	0
Bickers and Adams (1949), Boston, U.S.A.	7	6	1	0	0
Total	36	14	11	1	10

TABLE 2
A SUMMARY OF SIGNS IN 10 CASES PERSONALLY EXAMINED

Family	Identification	Age (yrs)	Approximate Mental Age (yrs)	Head Circumference (cm.)	Irregular Head	Asymmetrical Face	Squint	Thumbs Inturned	Spasticity of Legs	Contracture of Calf	Babinski Response	Other Signs
Bromyard (I)	Colin IV 5	19	3	57	+	+	+	+	+	++	−	a
	Michael IV 14	12	4	53	+	−	−	±	+	+	+	
	Glynn IV 15	9	2	53	+	+	−	+	+	+	+	b
	Martin IV 16	8	2	53	+	+	+	+	+	+	+	b
Thetford (II)	Maurice IV 5	31	3	60	+	+	−	+	+		+	
Northampton (III)	George III 4	38	2	56	+	+	−	±	++	++	±	c
	Sydney III 5	32	2	59·5	+	+	−	−	++	−	−	
	Alfred IV 3	17	2½	54·7	+	+	−	+	++	+	−	d
	Aubrey IV 6	13	3	53	+	+	−	−	+	−	−	
	Andrew IV 11	5	2½	53	−	+	+	−	+	−	−	

a = Spasticity of arms.
b = White speckling on irides.
c = Generalized irregular pigmentation.
d = Abnormal restlessness.

his hand or lying across his palm. It is uncertain if one or both thumbs were affected.

DISCUSSION

It must first be admitted that in no case personally examined was there unequivocal evidence of hydrocephalus. As all cases had obviously stabilized it did not seem justifiable to expose them to air studies. While many of the strands in this complex network of evidence relating these many cases are weak the author feels that, taken together, they permit the provisional inference that all these cases conform to a basic pattern, the most important lesion of which is aqueductal stenosis, that this is related to a mutation located on the X chromosome which is not manifest in the heterozygote, and that various other signs which may or may not be secondary to the main lesion are frequently present. There is great variation in expression within families and an even greater variation between families; these are summarized in Table 1. In advancing the suggestion that these disturbances are related to a mutation at a specific locus on the X chromosome, it is not intended to imply that the different mutations at this locus lead to identical functional derangements. The variation in severity between families, which is no greater than that often found in haemophilia, is not inconsistent with mutation *from* a single gene.

Anatomically the only lesion in the two cases studied in detail (Bickers and Adams, 1949; Edwards *et al.*, 1961) was a stenosis of the aqueduct: in the latter there was also a small pons and an apparent absence of the corticospinal tracts. How this developmental anomaly arises is far from obvious. Defective development of the lumen of a tube can arise either from an excessive growth of its wall, a defective growth of its lining, or an impairment in the forces normally maintaining patency. No abnormal deposits or structures were demonstrated in the wall. Although an early deficiency in cerebrospinal fluid flow can be postulated relevant observations are clearly unattainable. The evidence is consistent with a primary maldevelopment of the lining membrane, although this could be secondary to inadequate functional stimulation. The difficulties of suggesting any mechanism linking a genetic aberration and a stenotic aqueduct are hardly less than those of relating this lesion to the clinical syndrome, which is briefly reviewed in Table 2, and with which it appears to be associated.

The head is large, but even this primary sign is

unusual in that the enlargement is largely backward and outward, rather than upward, the head being oblong and irregular, and not, as is more usual in hydrocephalus, globular and smooth. Although ventricular dilatation in infancy will obviously explain the abnormality in size, it will not explain the shape, and still less the irregularity and asymmetry.

The face shows a generalized peculiarity, best described as a fleshy coarseness resembling that seen in photographs of professional boxers. This is not adequately explained as a result of apathy as it is more marked than in most mental defectives. The asymmetry can obviously not be explained in functional terms.

The hands pose a curious problem, the thumbs frequently showing a functional abnormality which is not associated with any marked neurological abnormality of the upper limbs, and is not easily dismissed as a non-specific finding in spasticity. The simplest explanation associates it with the unusually large area of cortical representation of the thumb. The abnormalities of the lower limbs, the well-known spastic-spindling which is frequently found in hydrocephalus, is probably of no diagnostic value in differentiation of various types of hydrocephalus, although it may suggest hydrocephalus when the head enlargement is not marked. The occasional co-existence of flexor plantar responses with marked spasticity is possibly more specific.

It is tempting to associate these peculiarities with a primary and highly specific disturbance of cortical control, and to associate this with a primary deficiency of the corticospinal tracts. This deficiency would be interpreted as either secondary to early ventricular dilatation or as an independent consequence of the same genetic shortcoming.

The syndrome as a whole cannot be adequately related to the focal lesion so far described. This hardly reduces the likelihood of the syndrome being a genuine entity as in the majority of morphological disturbances actuated by simple genetic mechanisms it is impossible to unravel the pedigree of causation by which a single metabolic aberration leads to multiple and apparently unrelated structural abnormalities. As an example of similar inadequately explained coexistent associations in a well-defined syndrome with a similar hereditary mechanism we may mention the association of mental deficiency and electrocardiographic abnormalities with Duchenne's type of muscular dystrophy (Dubowitz, 1961).

The inheritance seems clear cut and unequivocally sex-linked in the familial cases presented. Eight presumptively heterozygous women interviewed showed no suggestion of any partial manifestation. One was of very low intelligence, but this could easily be fortuitous; another was very intelligent. The facies, head shape, head size and gait were unremarkable in all. The segregation ratio is grossly abnormal with an excess both of affected males and heterozygous females. This is probably due to informal ascertainment of a rare and previously unrecognized syndrome. It is difficult to allow for this form of bias. If such disturbances in segregation were a consistent feature of mutation at this locus then very large pedigrees might be anticipated, and it would be surprising that these have not already been reported. If the segregation ratio is undisturbed the frequency of the syndrome in males will be three times the mutation rate, and the mutation rate is unlikely to greatly exceed 10^{-5}. As the incidence of hydrocephalus is approximately 10^{-3} this suggests that something of the order of less than 5% of male hydrocephalics may be due to this disorder. The recurrence rate in hydrocephalus is less than this, three series combined giving a recurrence incidence of one in 200 sibs (see Edwards *et al.*, 1961): it is possible that this syndrome may be the commonest variety of familial hydrocephalus if we exclude hydrocephalus secondary to spina bifida.

The syndrome may present with mental deficiency, the hydrocephalus being minimal with spasticity of the legs being the only definite physical sign. In this form it is probably very rare. Penrose (1938) in his study of 1,280 mental defectives with details of the mental state and physical abnormalities of all sibs, the parents and other affected relatives, found 66 cases of diplegia of prenatal origin. There was a slight excess of males (36 to 30) and a marked excess of consanguineous marriages (six). As only one family (propositi 52 and 53 in the series), with two diplegic male imbeciles, one normal male and two normal females, showed an exclusively male familial segregation, sex-linked diplegia, if it occurred at all in this series, was clearly far rarer than autosomal recessive diplegia.

SUMMARY

A series of cases of a syndrome consisting of mental deficiency, a slightly enlarged irregular head, spasticity with wasting and contractures limited to the legs and a curious facies is reported. Frequently associated findings include flexion deformity of the thumbs and a parodoxical plantar reflex which is flexor in spite of marked spasticity. It is suggested that this syndrome represents a pattern of signs found in conjunction with a variety

of aqueductal stenosis related to a mutation on the X chromosome.

I am most grateful to Dr. Clifford Parsons, Dr. I. H. Gosset, Dr. Christopher Ounsted, Professor L. S. Penrose and Dr. M. J. Peto for their introductions to these families, and to the staff of the Children's Hospital, Birmingham, for permitting me to quote results of investigations and to duplicate photographs.

References

Bamatter, F. (1949). Acquisitions récentes concernant les hydrocéphalies inflammatoires chez l'enfant. Travail d'habilitation de la faculté de Medicine de Genève (dactylographié). 87. (Quoted by Borle.)

Bickers, D. A. and Adams, R. D. (1949). Hereditary stenosis of the aqueduct of Sylvius as a cause of congenital hydrocephalus. *Brain*, **72**, 246.

Borle, A. (1953). Sur l'étiologie de l'hydrocéphalie congénitale. À propos d'un cas d'hydrocéphalie concordante chez des jumeaux univitellins. *J. Génét. hum.*, **2**, 157.

Dubowitz, V. (1961). *In* Report of symposium on muscular dystrophy. *Lancet*, **1**, 275.

Edwards, J. H., Norman, R. M. and Roberts, J. M. (1961). Sex-linked hydrocephalus. *Arch. Dis. Childh.*, **36**, 481.

Gellman, V. (1959). Congenital hydrocephalus in monovular twins. *Ibid.*, **34**, 274.

Penrose, L. S. (1938). A clinical and genetic study of 1,280 cases of mental defect. *Spec. Rep. Ser. med. Res. Coun.* (*Lond.*), No. 229.

—— (1946). Familial data on 144 cases of anencephaly, spina bifida and congenital hydrocephaly. *Ann. Eugenics*, **13**, 73.

Perez, M. L. and Linger, L. (1947). Hidrocefalia fetal a repeticion. *Rev. méd. cubana*, **48**, 280.

Zimmer, K. (1952). Über familiäres Auftreten von Hydrozephalus. *Geburtsh. u. Frauenheilk.*, **12**, 447.

HAEMOLYTIC ANAEMIA IN OSTEOPETROSIS

A REPORT OF TWO CASES

BY

H. GAMSU, J. LORBER and JOHN RENDLE-SHORT*
From the Department of Child Health, University of Sheffield

(RECEIVED FOR PUBLICATION JANUARY 30, 1961)

The anaemia so frequently found in cases of osteopetrosis in children has been generally regarded as being due to poor development of the bone marrow cavity by failure of absorption and organization of primitive chondro-osteoid tissue (Warkany, 1959; Clifton and Frank, 1959; Aegerter and Kirkpatrick, 1958). In many cases, however, the severity of the anaemia has not corresponded with the radiological appearances of the medullary cavity, and alternative theories have been put forward to explain this discrepancy. Some workers have suggested that the anaemia is due to a primary bone marrow defect (McCune and Bradley, 1934), and others (Creveld and Heybroek, 1940) have postulated that the bone lesions and the anaemia are both part of a common developmental mesenchymal disturbance. Hepatosplenomegaly, a common feature of this disorder, has been taken to indicate increased extramedullary erythropoiesis, and in view of this, splenectomy in cases of osteopetrosis is considered therapeutically unsound.

Recently, however, doubt has been thrown on the above beliefs, and evidence is now accumulating that although the spleen in osteopetrosis may be a site of blood formation, blood destruction is also actively taking place in this organ. Increased destruction of red cells was demonstrated by Zetterström (1957) when he found a reduced survival time of red cells tagged with radioactive chromium in a 10-year-old patient with osteopetrosis. Engfeldt, Karlberg and Zetterström (1955) demonstrated a reduced red cell survival time of the patient's and donor's cells in a child of 6 years.

Sjölin (1959) noted a constant excess of nucleated red cells in the blood of four patients, and this, together with the presence of reticulocytosis, thrombocytopenia, and the absence of demonstrable haemolysing antibodies, led him to conclude that haemolysis and hypersplenism occurred in osteopetrosis. In a series of investigations on his cases, Sjölin (1959) demonstrated the presence of haemolysis. (1) Specimens of blood from the patients were labelled with radioactive chromium (Cr_{51}) and were injected into the patients and into 12 healthy adults. The apparent half life of the labelled cells in the patients was considerably shorter than in the healthy recipients. (2) Labelled blood from compatible donors was injected into the patients and into two healthy compatible recipients. Again, the survival time of the cells in the patients was much shorter than in the healthy recipients, indicating that the cause of the haemolysis was entirely extracorpuscular. Circulating antibodies were not found in the blood of these patients.

Splenectomy was performed on all four of Sjölin's cases, and post-operative red cell survival time was shown to be significantly increased in two. After splenectomy all four cases showed a rise of haemoglobin and of the platelet count, and a fall in the reticulocyte count. In one case this response was not sustained. In another, the results after splenectomy could not necessarily be accounted for by the operation alone as the patient had been given numerous blood transfusions before the procedure. In none of these cases did splenectomy seem to produce any ill effects, nor were any noted in two other instances of splenectomy cited by Sjölin (Frank, 1931; Gérard-Lefebre, Vandendorp and Benoit, 1952).

The Present Investigation

At the time that Sjölin's paper appeared, we had under our care an infant with osteopetrosis and were thus able to confirm some of Sjölin's findings by using one of his techniques. Previously, this infant's brother had been in the same unit, also with osteopetrosis. These two patients are the subject of this presentation. They were the children of young, healthy, unrelated parents. Their mother had five pregnancies, the second pregnancy terminating after three months in an abortion. Of the

* Present address: Department of Child Health, University of Queensland, Brisbane, Australia.

TABLE 1

SUMMARY OF HAEMATOLOGICAL FINDINGS IN CASE 1 DURING FIRST THREE MONTHS OF LIFE

Age (Days)	Haemoglobin (g./100 ml.)	R.B.C. (millions per c.mm.)	Nucleated R.B.C. per 100 W.B.C.	Reticulocytes (%)	W.B.C. per c.mm.	Differential (%)		Platelets per c.mm.	Transfusions (ml. of packed cells)
						Lymphocytes	Polymorphs		
10	4·6	1·5	5	—	6,700	96	3	'Normal'	—
11	—	—	—	—	—	—	—	—	20
21	3·7	—	—	—	—	—	—	—	—
22	—	—	—	—	—	—	—	—	100
25–37	—	—	—	—	—	—	—	—	100
38	13·6	4	8	—	5,600	82	16	154,000	—
43	5·6	—	—	—	—	—	—	—	—
46	—	—	—	—	—	—	—	—	130
50	4·4	—	—	—	—	—	—	—	150
90	3·3	1·1	13	7·8	9,000	65	19	9,000	—
92	—	—	—	—	—	—	—	—	180
93	11·8	3·4	—	5·5	10,500	—	—	10,500	—

four children born alive, the first and fourth had osteopetrosis, the second is a normal girl of 6 years of age, the third was born at home, weighing 3 lb. 2 oz., and died at the age of 3 days. No haematological examination or autopsy was performed on this infant.

Neither parent shows any abnormal features on radiographs taken of their long bones, spines and skulls. There is no history of osteopetrosis in other members of the family.

Case 1

Stephen was born four weeks prematurely and weighed 4 lb. 4 oz. at birth. At the age of 4 days he was jaundiced, but this gradually faded and was no longer present at the age of 11 days. At the age of 10 days, he had a slight epistaxis and was pale. At this stage a purpuric rash was present over the face, trunk and limbs.

Investigations. The haemoglobin was 4·6 g./100 ml., red blood cells numbered 1·5 million per c.mm. (Table 1). There were 6,700 white cells per c.mm., 96% of which were lymphocytes, 3% polymorphonuclears and 1% eosinophils. Five nucleated red cells were seen to every 100 white cells. Platelets were not counted, but appeared normal. The mother's blood group was A rhesus positive and that of the infant was B rhesus positive. The Coombs direct antiglobulin test on the infant's blood was negative and the Wassermann reaction of both mother and infant was negative. Bleeding time was two and a half minutes, clotting time four minutes.

Subsequent Course. The infant was given 20 ml. blood and 10 days later when the haemoglobin had fallen to 3·7 g./100 ml., a further blood transfusion of 100 ml. blood was given.

At 5½ weeks the purpura was still marked. The haemoglobin just after a blood transfusion was 13·6 g./100 ml., but during the next five days the level had fallen to 5·6 g./100 ml. The infant was given a total of five blood transfusions during the first two months of his life.

At the age of 3 months he was transferred to the Sheffield Children's Hospital. He had a purpuric rash and his liver and spleen were both palpable. He was very pale, the haemoglobin being only 3·3 g./100 ml. The platelets numbered 9,000 per c.mm. and reticulocytes 7·8% on admission. He was given a transfusion of 180 ml. blood, but his haemoglobin continued to fall and one month later a further 180 ml. blood was given. Examination of the bone marrow showed appreciable, though low erythropoietic activity in the specimen from the scapula. The marrow of the tibia and iliac bone was strikingly hypoplastic. Radiographs of the skeleton showed generalized osteopetrosis. The infant was given intramuscular cortisone for four weeks in an attempt to retard the development of anaemia and it seemed that shortly after treatment had been started and for some six months after cortisone had been withdrawn, the level of haemoglobin remained within normal limits and no transfusions were necessary. Purpura, too, was not so marked during this time.

At the age of 4 months the child was readmitted with gastro-enteritis. This cleared up within two days, but one week later his urine showed a positive reaction to urobilin and urobilinogen and the output of urobilinogen in the stools was normal (2·2 mg. in 24 hours). The platelet count was 190,000 per c.mm.; the haemoglobin 10 g./100 ml., and a reticulocyte count of 6·5% was noted. No immune antibodies were found and the direct Coombs test was negative. The red cells showed increased resistance to complete haemolysis when suspended in serial dilutions of saline (haemolysis was 59% in a concentration of saline of 0·35% and 19% in a concentration of saline of 0·45%), but there was constant haemolysis of 10% in saline which was hypertonic (0·65%, 0·75%).

At the age of 5 months he presented with a history of jaundice for 10 days. His urine was dark and contained bilirubin, bile salts and urobilinogen and his faeces were pale. At that time it was considered likely that he had homologous serum jaundice from one of his previous blood transfusions.

During the rest of his life he required two or three monthly blood transfusions. His haemoglobin fell despite a persistent reticulocytosis of 3-5%. His liver and spleen became large and hard. He became blind

with roving nystagmus and marked optic atrophy, and also deaf. He twice fractured his tibia as a result of a trivial injury. The platelets numbered 13,000 per c.mm. at the age of 1 year and thereafter the platelet count ranged between 10,000 and 200,000 per c.mm. for the rest of his life. In all he received 32 blood transfusions before he died at the age of 6 years.

Autopsy. Naked eye examination revealed the following relevant findings:

Respiratory tract. There was mucopurulent material in the nose and nasopharynx. The lungs did not collapse on opening the chest and there were a large number of greyish areas on cut section.

The liver. This weighed 580 g. and appeared normal.

The spleen. This weighed 255 g. and was large and firm, cutting almost like fibrous tissue.

Skeletal system. All bones which were extremely hard and brittle, were surrounded by large masses, and at first sight these seemed to be large tumour deposits. On closer examination they were seen to be red plaques in the periosteum which almost covered the ribs and which were also present over the skull.

Lymph nodes. These were slightly enlarged, particularly the hilar, retroperitoneal and iliac glands, which were brownish-red in colour.

The brain. The external surface was normal.

Histological findings were as follows:

Bones. Sections of the bones showed large masses of osteoid and matrix with irregular calcification and little in the way of bone marrow production. Multiple small haemorrhages were present in the periosteum of all sections examined.

The brain and lungs. These showed evidence of old haemorrhage and increased pigment deposition.

Lymph nodes. All showed increased pigment deposition.

Spleen and liver. There was no definite evidence of erythropoiesis in either of these organs.

Iron staining. Massive quantities of iron were present in the parenchymal cells of the liver. In the lungs there was irregular distribution of iron and there was some deposition at the site of previous small haemorrhages. Small focal areas of pigment were present in the periosteum of all bones. A large quantity of iron was present in the lymph nodes and was especially marked in the cells lining the sinuses.

Case 2

Paul was born on November 26, 1959, after a normal pregnancy of 36 weeks, and weighed 4 lb. 2 oz. The haemoglobin at birth was 19·7 g./100 ml. The infant became progressively paler and at the age of 18 days his haemoglobin had dropped to 10 g./100 ml. A whole body radiograph showed a generalized increase in bone density and a lack of differentiation between cortex and medulla. The appearances were typical of osteopetrosis.

Subsequent Course. When 3 weeks old the baby was transferred to the Sheffield Children's Hospital. He was then extremely pale, the haemoglobin being 6·6 g./100 ml. A purpuric rash was present over the face and trunk and there were scattered petechiae over the hard palate. The liver and spleen were both palpable and firm. The optic discs appeared normal.

A peripheral blood smear showed a leucoerythroblastic reaction with nucleated red cells and immature white cells. Blood culture was sterile. At the age of 24 days the serum indirect bilirubin was 4·5 mg./100 ml. The urine contained a slight excess of urobilin and urobilinogen, but no bilirubin was present. Faecal stercobilin in a single specimen was 77 mg./100 ml.

At the age of 23 days a transfusion of 120 ml. of packed cells was given. Two weeks after this transfusion the haemoglobin had fallen to 3·7 g./100 ml. and the baby received a further transfusion of 150 ml. packed cells. After these transfusions the spleen was more easily palpable for some days, but it became smaller and more difficult to feel again as the baby became more anaemic. The direct Coombs test was negative when performed on a fresh warm blood sample, but more detailed tests for haemolysis and haemagglutinins were difficult to interpret because the baby seemed to be producing very few erythrocytes and most of the red cells in his peripheral blood were those of his blood donors. Tests for haemoglobin binding showed that haemoglobin was bound to β globulin and albumin. No haptoglobulin was present.

The rapid development of anaemia after each transfusion, the constant reticulocytosis (see Table 2) and the raised serum bilirubin, all suggested that haemolysis was taking place.

When the infant was 7 weeks old, tests were done using his own red cells tagged with radioactive chromium (Cr_{51}) which were injected into the infant and his father, to see whether the cells were being haemolysed more rapidly in the infant. A full description of this investigation is given. After this procedure another transfusion of 130 ml. of packed cells was given.

When he was 8 weeks old the baby's general condition deteriorated suddenly. Muscle tone in the limbs was increased and he began to have frequent generalized convulsions. The fontanelle was tense and the infant became extremely pale. He was thought to have had a cerebral haemorrhage resulting from the thrombocytopenia. Prednisolone in a dose of 10 mg. daily was given in an attempt to influence the platelet count. Phenobarbitone gr. ½ twice a day was also given, but the fits continued, and during one such fit, two days after their appearance, the baby died.

Radioactive Chromium Studies. Red cells taken from the infant were tagged with approximately 12 microcuries of Cr_{51} and were resuspended in 21 ml. of saline: 4 ml. of the suspension of tagged cells were injected into the baby and 14 ml. into the baby's father. Blood samples were taken at regular intervals from the infant and his father; in the former for five days after injection of tagged cells, and in the latter for seven days.

Agglutination tests on the original sample from the baby showed that the blood that had been tagged was

TABLE 2

SUMMARY OF HAEMATOLOGICAL FINDINGS IN CASE 2

Age (days)	Haemoglobin (g./100 ml.)	R.B.C. (millions per c.mm.)	Nucleated R.B.C. per 100 W.B.C.	Reticulocytes (%)	W.B.C. per c.mm.	Differential (%)		Platelets (per c.mm.)	Transfusions (ml. of packed cells)
						Lymphocytes	Polymorphs		
1	19·7	—	—	—	—	—	—	—	—
18	10	—	—	—	—	—	—	—	—
20	9·7	3·3	—	—	7,200	70	27	'Normal'	—
23	6·6	—	—	—	—	—	—	—	120
24	13·9	4·25	'some nucleated red cells'	—	4,500	86	11	94,000	—
26	12·6	—	—	—	—	—	—	—	—
27	11	—	—	—	—	—	—	—	—
32	5·8	2·1	—	—	6,500			50,000	—
34	5·5	2·0		2	7,000	85	15	49,000	—
37	3·7	1·3	—	2·5	5,500	—	—	41,000	150
39	15·2	4·3	2	2·1	4,000	79	17	108,000	—
40	15·1	4·6	—	2·1	5,000			83,000	—
42	11·4	3·4	? some nucleated red cells	2·4	10,000	87	10	72,000	—
46	8·1	2·5	some nucleated red cells	2·5	7,000	87	10	40,000	
48	8·6	—	—	—	—	—	—	—	—
50	—	—	—	—	—	—	—	—	130
51	14·7	—	—	—	—	—	—	—	—
53	10	—	—	—	—	—	—	—	—
55	6·7	—	—	—	—	—	—	—	—

not the infant's own blood, but consisted entirely of donor cells from the transfusions he had been given.

The results were expressed as the ratio of activity in the saponized whole blood sample to the activity in the counting standard. The latter was made up of a dilution of one part in 100 from the saponized suspension of tagged cells. Loss of activity in the counting solution was corrected by using as the standard count the mean count observed over the first five days before loss of activity was apparent.

The results are plotted on the attached graph (Fig. 1), in which the rapid decline of activity in the patient's blood as compared to that in the father can readily be seen.

The time to half activity was deduced from the best straight lines drawn through the points plotted logarithmically and was estimated as 2·7 days in the infant and 21 days in the father.

Autopsy. The body was that of a small pale infant with numerous petechiae in the skin, particularly of the scalp. The main naked eye changes were found in the brain and skeletal system. *The brain* was grossly oedematous. A large area of superficial thrombosis with an underlying haemorrhage was found over the right hemisphere.

The bones were of a deep red colour and were thickened. The ribs were acutely angulated at the costovertebral joints. Large dark red areas were present under the periosteum of the inner table of the skull.

The gross appearance of the *liver* and *spleen* was normal. The liver weighed 116 g. and the spleen 7 g.

A few petechiae were seen in both *lungs*.

Histological studies were carried out.

Brain. Slightly increased subependimal gliosis was present with haemorrhages around the cerebellum and small haemorrhages in the deeper parts of the brain. The meninges were unusually thick and contained a large number of lymph and plasma cells.

Bone. A rib, skull bone, vertebra and phalanges of a toe were examined, and all showed that the bone consisted almost entirely of osteoid. Maturation seemed

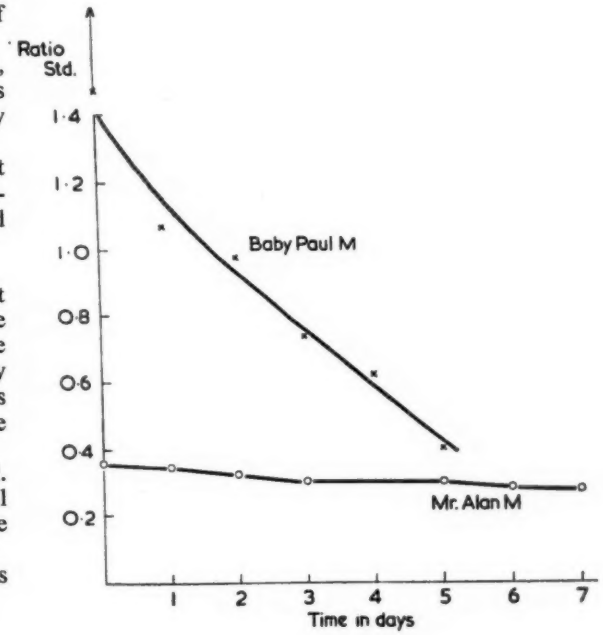


FIG. 1.—Results of serial blood tests for radioactivity after injection of Cr_{51} into Case 2 and into his father. Results are expressed as a ratio of activity in the saponized whole blood sample to the activity in the counting standard. For details, see text.

to be normal until the stage of disappearance of the matrix when further maturation seemed to stop, and the entire shaft was filled with osteoid bone. The cavities of the osteoid were filled with a normal amount of haemopoietic tissue. The subperiosteal red areas over the inner table of the skull, which had been seen at autopsy, proved to be haemorrhages within the periosteum.

Spleen and *liver*. There was no evidence of increased erythropoiesis.

Iron staining. This was increased and was most marked in lymph nodes, testis, in the central involuting area of the adrenal and in the parenchymal cells of the liver. Iron staining was also present to a lesser extent in the brain and lungs.

Tissue samples were analysed for the presence of radioactivity. This was expressed as a percentage of the administered dose of radioactive chromium per gramme of tissue (Table 3).

The value for the spleen is clearly the highest.

TABLE 3
ANALYSIS OF TISSUE SAMPLES FOR SIGNS OF RADIOACTIVITY

Specimen	Fraction of Total Dose per Gramme
Mediastinal lymph node	$0{\cdot}85 \times 10^{-3}$
Cervical lymph node	$1{\cdot}07 \times 10^{-3}$
Spleen	$3{\cdot}33 \times 10^{-3}$
Right lobe of liver	$0{\cdot}52 \times 10^{-3}$
Left lobe of liver	$0{\cdot}59 \times 10^{-3}$
Vertebra	$0{\cdot}42 \times 10^{-3}$
Rib	$1{\cdot}01 \times 10^{-3}$
Iliac crest	$0{\cdot}65 \times 10^{-2}$
Spine	$1{\cdot}43 \times 10^{-3}$

Discussion

Both cases presented the classical features of haemolytic anaemia. Reticulocytosis and nucleated red cells were noted in both. Haemolysis was also strongly suggested by the rapid development of anaemia after each blood transfusion. In both cases there was an excess of urobilin in the urine and in Case 2 the level of stercobilin was high, and the indirect bilirubin level of the blood was raised. Unfortunately, the development of homologous serum jaundice at the age of 5 months makes it difficult to evaluate the full significance of the bile pigment investigations in Case 1. Further evidence of haemolysis was provided by the test of haemoglobin binding which was described by Neale, Aber and Northam (1958). They found that in states of intravascular haemolysis, haptoglobulin. to which haemoglobin is normally bound for transport from the blood after lysis, was absent, and that alternative binding to β globulin took place. In Case 2, no haptoglobulin was demonstrated, and the haemoglobin was found to bind with β globulin and albumin. The short life span of the red cells labelled with radioactive chromium is additional evidence for increased blood destruction in Case 2; and the accumulation of radioactivity in the spleen is suggestive, although by no means definite evidence, that most of the blood destruction was taking place in this organ.

The signs of haemolytic anaemia were only present from the age of 4 months in Case 1 and developed shortly after birth in Case 2 and it is surprising when one considers the severity of the anaemia in the latter that the infant was not anaemic at birth. This suggests some humoral factor present in the maternal blood which has kept the development of anaemia in abeyance *in utero*. In Case 1, it seems possible that the marrow could only respond to developing anaemia when the child was 3 months of age.

Although reduced in amount, haemopoiesis was shown to be present in marrow samples from Case 1 and the post-mortem appearances of the bone in Case 2 showed that there were large areas of functioning marrow in the medulla. It is unlikely that the anaemia in these cases could have been caused solely by defective haemopoiesis. Also, although haemorrhages were present in both cases in the form of purpura with slight epistaxis and there were multiple small haemorrhages in all tissues examined histologically, these could hardly be held responsible for the severe anaemia developing so rapidly after each blood transfusion. It is interesting to note that purpura was present in Case 1, even when the platelet count was normal and it is noteworthy that Aherne (1960) mentioned that in his case the same situation obtained. He described the platelets of his case as being morphologically abnormal, but this feature was not found in our patients. The disappearance of the purpura and the maintenance of a normal haemoglobin level after cortisone therapy in Case 1 is difficult to explain, and it is tempting to ascribe this response to the therapy. Because of the apparent temporary success of this treatment in this case and because of the known efficacy of steroid therapy in haemolytic anaemia, the same treatment was considered in Case 2, but he died before an adequate course could be given.

Although in Sjölin's cases, erythropoiesis in the spleen was described as being lively, in our patients and in the case described by Aherne (1960) no evidence of increased haemopoiesis was found. It is therefore not invariably the case that the spleen is an important organ of haemopoiesis in osteopetrosis. It seems likely that thrombocytopenia played at least some part in the production of the

haemorrhages found in both patients, particularly in Case 2. Sjölin found that splenectomy in his cases resulted in correction of the platelet count. It seems that splenectomy is strongly indicated in cases of malignant osteopetrosis, especially in the presence of haemorrhagic manifestations and anaemia.

Summary

Two cases of osteopetrosis in siblings are presented. They both had the malignant form of the disease, with radiological changes and severe anaemia in the neonatal period.

Reticulocytosis and a high proportion of nucleated cells were found in both patients, and this, together with a raised bilirubin level in the blood of Case 2 and the rapid development of anaemia following transfusion in both children, suggested that haemolysis was taking place.

The rapid disappearance of radioactivity in the blood of Case 2 after injection of radioactive chromium (Cr_{51}), and changes in haemoglobin protein binding are presented as further evidence for the presence of haemolysis.

Our thanks are due to Professor R. S. Illingworth for permission to publish these cases, to Dr. M. Middleton who referred them to us, to Dr. I. Dunsford for the agglutination tests, Dr. G. Blomfield and Dr. N. T. Nicol for the radioactive chromium test, and to Dr. J. Emery for the autopsy findings. We also thank Mr. A. F. Foster and Mr. J. F. V. Larway for the illustration.

References

Aegerter, E. E. and Kirkpatrick, J. A. (1958). *Textbook of Orthopaedic Diseases*, p. 115. Saunders, Philadelphia and London.

Aherne, W. (1960). A case of osteopetrosis (Albers-Schönberg) with intercurrent pneumocystis pneumonitis. *Arch. Dis. Childh.*, **35**, 495.

Clifton, W. M. and Frank, A. (1959). Osteopetrosis: Marble bones. In *Practice of Paediatrics*, ed. I. McQuarrie, and J. Brennemann, vol. 4, chap. 23, section 2, p. 19. Prior, Hagerstown, Maryland.

Creveld, S. van and Heybroek, N. I. (1940). On Albers-Schönberg's disease (marble bones). *Acta paediat.* (*Uppsala*), **27**, 462.

Engfeldt, B., Karlberg, P. and Zetterström, R. (1955). Studies on the skeletal changes and on the etiology of the anaemia in osteopetrosis. *Acta path. microbiol. scand.*, **36**, 10.

Frank, E. S. (1931). Marmerbeenziekte (Osteopetrosis). *Ned. T. Geneesk*, **75**, 5794.

Gérard-Lefebre, Vandendorp, F. and Benoit, M. (1952). Essai de greffe osseuse suivie de splénectomie chez un nourrisson atteint de maladie d'Albers-Schönberg à forme maligne précoce (Présentation de malades). *Arch. franç. Pédiat.*, **9**, 538.

McCune, D. J. and Bradley, C. (1934). Osteopetrosis (marble bones) in an infant. Review of the literature and report of a case. *Amer. J. Dis. Child.*, **48**, 949.

Neale, F. C., Aber, G. M. and Northam, B. E. (1958). The demonstration of intravascular haemolysis by means of serum paper electrophoresis and a modification of Schumm's reaction. *J. clin. Path.*, **11**, 206.

Sjölin, S. (1959). Studies on osteopetrosis, II. Investigations concerning the nature of the anaemia. *Acta paediat.* (*Uppsala*), **48**, 529.

Warkany, J. (1959). Osteopetrosis. In *Textbook of Pediatrics*, 7th ed., ed. W. E. Nelson, p. 1240. Saunders, Philadelphia and London.

Zetterström, R. (1957). Osteopetrosis (marble bone disease): Clinical and pathological review. *Mod. Probl. Pädiat.*, **3**, 488.

A HAEMOLYTIC-URAEMIC SYNDROME IN INFANCY

BY

JOAN GRIFFITHS and K. G. IRVING
Paediatrician, and Clinical Pathologist, Johannesburg

(RECEIVED FOR PUBLICATION MARCH 3, 1961)

In 1955 Gasser, Gautier, Steck, Siebenmann and Oechslin described five children, aged 2 months to 7 years, with acquired haemolytic anaemia, bizarre poikilocytes and renal insufficiency. Three had thrombocytopenia and all the patients died.

In 1957 Allison described six infants suffering from acquired haemolytic anaemia, proteinuria, haematuria and uraemia, who showed a characteristic and diagnostic blood picture with erythrocyte fragmentation, spherocytosis and thrombocytopenia. Only two of these patients died; the others recovered completely.

Aherne (1957) described two patients, aged 4½ months and 10 years, whose blood pictures also showed distorted and abnormal erythrocytes and who had a haemolytic anaemia, haematuria and uraemia with eventual recovery. He suggested that they were examples of non-fatal Gasser's syndrome.

Within 18 months of our becoming aware of the existence of this syndrome we have encountered what we believe to be three examples of it, and we feel that the condition is probably more common than is generally recognized. For this reason the three cases are presented, and the clinical progress of the infants is recorded in some detail.

Case Reports

Case 1. J.S., a female child, was 9½ months old. Pregnancy, delivery and postnatal progress were normal. She was first seen on February 14, 1959, when suffering from diarrhoea and severe intermittent abdominal pain of four days' duration. She had received small doses of a sulphonamide preparation. The stools were watery for two days; they then became blood-stained but infrequent, although the patient was repeatedly straining. On February 14 she began, in addition, to vomit.

On examination the child was screaming and anxious-looking. It was impossible to be certain that the abdomen was normal and on rectal examination the finger encountered what was thought to be the apex of an intussusceptum. However, on admission to hospital she passed a single normal stool, and a barium enema revealed no abnormality as far back as the middle part of the ascending colon.

The patient did not appear to be very ill and physical examination was essentially negative. Blood pressure was 90/50 mm. Hg. During the first 36 hours in hospital she was mildly pyrexial, she vomited occasionally and passed several blood-stained, watery stools. Her condition then deteriorated suddenly. She had a convulsion which lasted for 10 minutes, and then she became unconscious, opisthotonic and dehydrated. There were no localizing neurological signs. Apart from a raised protein value (95 mg. per 100 ml.) the cerebrospinal fluid was normal. However, her blood urea was elevated (135 mg. per 100 ml.) and the urine showed protein and microscopic blood. The haemoglobin was 11·2 g. per 100 ml. and the leucocyte count 13,700 per c.mm. with a definite polymorphonuclear 'shift to the left' (polymorphonuclears 54%, monocytes 7%, lymphocytes 37%, metamyelocytes 1%, myelocytes 1%). The appearance of the red cells was suggestive of an early haemolytic process with 'burr' cells and microspherocytes present in moderate numbers. Anisocytosis was also present. Platelets were approximately 135,000 per c.mm.

The significance of the blood picture was not immediately realized, especially in view of the fact that the serum bilirubin was not raised, although clinically the skin had been observed to have an orange tinge. The patient remained gravely ill for five days with opisthotonus and stupor, and, despite intravenous fluid, she was oliguric.

On the fourth day in hospital (February 18), two days after her sudden onset of stupor, the haemoglobin level had fallen to 8·0 g. per 100 ml. The red cell appearances were now very striking. Anisocytosis and poikilocytosis were well marked and there were many fragmented erythrocytes, polychromatic cells and microspherocytes. Macrocytes and nucleated red cells were also present in small numbers. Reticulocytes were 4%. A definite thrombocytopenia was now present, platelets being approximately 60,000 per c.mm. Heinz bodies were not found in supravitally stained preparations.

No purpura was present at this or at any other stage of the illness nor was there any enlargement of liver or spleen. A transfusion of 200 ml. blood was given and the haemoglobin level rose to 12·8 g. per 100 ml. Treatment with prednisone was begun. Meanwhile her electrolyte and fluid balance required careful management (Table 2) for the five days of oliguria until on her

seventh hospital day there was a marked diuresis. However, proteinuria and elevated blood urea levels persisted, but there was a gradual return to normal of her level of consciousness. Unfortunately, the urine became heavily infected with coliform bacilli which proved resistant to treatment except by kanamycin. The red cell abnormalities were now far less marked, but, 10 days after the initial blood transfusion, a second one was required because the haemoglobin level had fallen to 9·4 g. per 100 ml. At this time she was again pyrexial and mildly hypertensive (blood pressure 120/40 mm. Hg).

After this second blood transfusion her condition improved steadily, although the proteinuria persisted and she continued to pass watery stools intermittently, and for a few days she showed a further elevation of systolic and diastolic blood pressure (blood pressure 120/90 mm. Hg). At no time in the illness were any abnormalities of the fundi detected.

After three and a half weeks the blood urea, having been consistently between 100 and 170 mg. per 100 ml. (even after the urinary output became reasonably good) fell to a normal level and the haemoglobin was 14·0 g. per 100 ml. Five weeks after admission she was discharged from hospital and has remained well since.

Pathological Investigations. The results of the main haematological and biochemical investigations at various times during the illness are given in Tables 1 and 2.

In addition to these, many other investigations were carried out. Coagulation, bleeding and prothrombin times were found to be normal. The Wassermann reaction, the direct antiglobulin (Coombs) test and standard agglutination tests were all negative and the quantitative osmotic fragility test gave results within the limits of normality. One blood culture taken on February 16 remained sterile. A bone marrow sample (tibia) on February 20 was hypercellular with a normoblastic reaction and normoblastic erythropoiesis. Platelet formation appeared to be normal and there was no evidence of malignancy. Surgical biopsy of muscle and skin showed no significant pathological changes.

Throughout the illness there was persistent proteinuria, and as already described there was at one stage an infection of the urine by coliform bacilli. Haematuria was marked at the onset, but red cells became scanty from the tenth day. After discharge all urinary abnormalities disappeared. Examination of the faeces on February 15 revealed numerous leucocytes and red cells, but no pathogenic bacteria were isolated. A similar result was obtained from a stool examination on February 28, 1959. In July 1960, the blood was found to have a normal glucose-6-phosphate dehydrogenase activity (method of Motulsky and Campbell).

Case 2. E.D., a female child, was 6½ months old. Her birth was normal, but induced 10 days before term owing to mild toxaemia. Although the mother was rhesus negative and the father rhesus positive, no antibodies developed during this the mother's first pregnancy. She was quite well until September 22, 1959, when her mother noticed that she was not using her left arm. Her doctor examined her, but could find no abnormality of the nervous or any other system. The condition cleared up without treatment within a day. She remained well until October 1 when her doctor was again called in to see her, as she was pale and fretful and was vomiting after each feed. Her temperature was 103° F. (39·4° C.) and her haemoglobin was only 5·5 g. per 100 ml.; the total leucocyte count was raised to 18,600 per c.mm., reticulocytes 3·1%, platelets 250,000 per c.mm., and the serum total bilirubin was 1·4 mg. per 100 ml. She had gross proteinuria and microscopy revealed many red cells in the centrifuged deposit, together with numerous granular casts.

The clinical picture suggested an acute haemolytic episode and the child was transfused with 250 ml. blood which raised her haemoglobin to 11·0 g. per 100 ml. She was also treated with 'largactil' (chlorpromazine) syrup and tetracycline. There was immediate but short-lived improvement. She soon became pale again and began to vomit repeatedly. Haemoglobin fell to 7·0 g. per 100 ml. and she was referred to our care on October 7, 1959, and admitted to hospital.

At this time she was pale and mildly jaundiced, but she appeared to be well nourished. She had a temperature of 102° F. (38·9° C.). There was no evidence of purpura. The liver, spleen and lymph nodes were not

TABLE 1

HAEMATOLOGICAL INVESTIGATIONS: CASE 1

Date	Haemoglobin (g./100 ml.)	Leucocytes per c.mm.	Platelets per c.mm. (Normal Range 150,000–400,000)	Reticulocytes
16.2.59	11·2	13,700	135,000	
18.2.59	8·0	16,300	60,000	4%
19.2.59	12·8			
20.2.59	12·2	18,000	170,000	
22.2.59	11·6		190,000	
23.2.59	10·8			
25.2.59	10·0		Plentiful	
28.2.59	9·4	51,000	Plentiful	
2.3.59	17·0	44,000	Plentiful	
4.3.59	19·3	20,400	Plentiful	
9.3.59	14·5	16,800	Plentiful	Less than 1%
13.3.59	14·0	20,700	Plentiful	Less than 1%

TABLE 2

BIOCHEMICAL INVESTIGATIONS: CASE 1

Date	Serum Sodium (mEq/l.) (Normal Range 141–152)	Serum Potassium (mEq/l.) (Normal Range 4·1–5·6)	Blood Urea (mg./100 ml.) (Normal Range 20–40)	Serum Bilirubin (mg./100 ml.) (Normal Range 0·1–0·8)
16.2.59	133	5·4	135	0·6
17.2.59	131	5·8	120	
19.2.59	131	5·2	160	0·5
20.2.59	131	4·6	135	
22.2.59	133	5·1	165	
23.2.59	137	4·9	170	
28.2.59	147	5·6	115	
2.3.59	137	5·4	137	
4.3.59			160	
9.3.59		5·4	45	
13.3.59			30	0·5

enlarged. There was no inflammation of the ears or throat and examination of the cardiovascular, respiratory and nervous systems revealed no abnormalities. The blood pressure was 120/70 mm. Hg.

The haemoglobin was 6·4 g. per 100 ml. and the total leucocyte count was 22,000 per c.mm. (polymorphonuclears 33%, monocytes 4%, lymphocytes 58%, eosinophils 1%, metamyelocytes 2%, myelocytes 2%). The platelet count was approximately 140,000 per c.mm. The red cell appearances were very similar to those described in Case 1 with well-marked polychromasia, anisocytosis and poikilocytosis. Microspherocytes and fragmented erythrocytes were present in moderate numbers and there was an erythroblastaemia (10 nucleated red cells per 200 leucocytes). There was gross proteinuria and about 30 red cells per high power field were found in the urinary centrifuged deposit. Leucocytes and casts were not detected. The blood urea was 155 mg. per 100 ml.

The patient was transfused with 300 ml. blood, given prednisone and maintained on intravenous therapy for two days until all vomiting ceased. After transfusion there was a dramatic improvement and she passed a satisfactory volume of urine. Her haemoglobin level rose to 19·0 g. per 100 ml.

On the sixth hospital day her blood pressure increased to 140/100 mm. Hg, but it fell to 88/60 mm. Hg three days later. On the twelfth hospital day she developed a gastro-enteritis which responded to treatment with chloramphenicol and penicillin.

Apart from this rather minor set-back she made steady progress, the blood urea falling to 25 mg. per 100 ml. after two weeks in hospital. A week later marked proteinuria persisted, but the number of red cells found microscopically was minimal and the urine was virtually normal by November 5. Red cell abnormalities were far less marked by October 14, and on October 25 the erythrocytes showed no significant pathological changes. After four weeks she was discharged from hospital clinically well, but with a rather poor appetite. She continued to improve after discharge, and on November 5 the haemoglobin level was 12·8 g. per 100 ml. and the blood urea was 30 mg. per 100 ml.

TABLE 3
HAEMOGLOBIN AND TOTAL LEUCOCYTE ESTIMATIONS: CASE 2

Date	Haemoglobin (g./100 ml.)	Platelets per c.mm. (Normal Range 150,000–400,000)	Total Leucocyte Count per c.mm.
7.10.59	6·4	140,000	22,000
8.10.59	19·0		
10.10.59	19·2		
14.10.59	16·0	50,000	
19.10.59	15·2	Plentiful	
21.10.59	12·4		12,300
23.10.59	15·6	Plentiful	
5.11.59	12·8		

TABLE 4
BIOCHEMICAL INVESTIGATIONS: CASE 2

Date	Serum Sodium (mEq/l.) (Normal Range) 141–152)	Serum Potassium (mEq/l.) (Normal Range) 4·1–5·6)	Blood Urea (mg./100 ml.) (Normal Range) 20–40)
7.10.59	133	4·9	155
10.10.59	131	5·2	65
14.10.59			50
19.10.59			45
21.10.59	142	6·2	25
5.11.59			30

Pathological Investigations. The main haematological and biochemical investigations are summarized in Tables 3 and 4.

Only on two occasions, October 7 and 14, were the platelets found to be slightly or definitely reduced in numbers—approximately 140,000 and 50,000 per c.mm. respectively. At all other times they were plentiful.

The Wassermann reaction and the direct antiglobulin (Coombs) test were negative and Heinz bodies were not found. As the father of this child was of Mediterranean origin a search for abnormal haemoglobins was made, but none was found. A bone marrow examination on October 8 revealed a hypercellular marrow with a normoblastic reaction and normoblastic erythropoiesis. Many megakaryocytes were found and platelet formation appeared to be normal. There was no evidence of malignancy.

Case 3. A.S., a male child, was 1 year and 4 months old. His birth was normal, but he weighed only 4 lb. 10 oz. Although a sibling had required an exchange transfusion for erythroblastosis foetalis (mother rhesus negative and father rhesus positive) this child was not affected. In the first few months of life he developed infantile eczema which disappeared at the onset of this illness. He had been well until August 14, 1960, when he developed loose stools containing blood and mucus. He was admitted to hospital for a few days by his family doctor and received a sulphonamide preparation. He was intensely irritable and was thought to be mildly jaundiced and pale. He began to vomit on August 21, 1960, and had several vomits daily. His urine became yellow on August 23 and he developed bruises all over his body.

He was transferred to our care on August 25 and was found to be pale and intensely irritable with mild oedema of the eyelids. The skin showed a yellowish tinge, but the conjunctivae were clear. There were several bruises on each extremity and all over the trunk. There was no pyrexia and, despite his clinical anaemia, he vigorously resented physical examination. Spleen and lymph nodes were not enlarged, but the liver edge could be palpated. The gums were grossly swollen over four molars. There was no inflammation of the ears or throat, and the cardiovascular, respiratory and nervous systems revealed no abnormalities. Blood pressure was 110/74 mm. Hg. The haemoglobin was 5·6 g. per 100 ml. and the leucocyte count was 13,000 per c.mm. (polymorphonuclears 42%, monocytes 9%, lymphocytes 43%, eosinophils 4%, mast cells 1% and neutrophil metamyelocytes 1%). Platelet count was 51,000 per

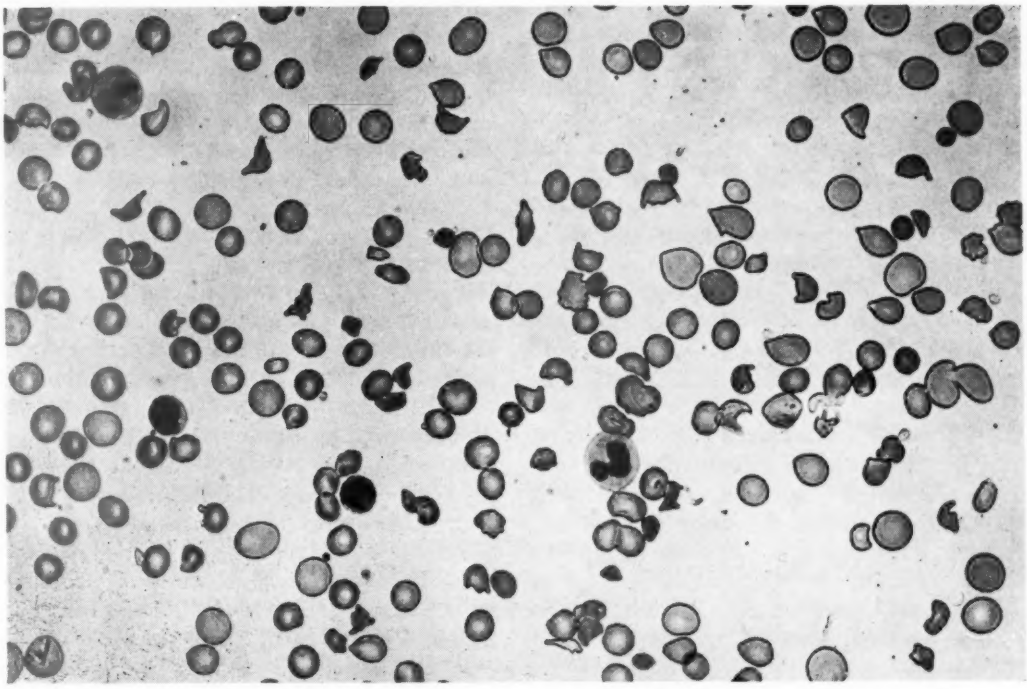


FIG. 1.—The peripheral blood appearances of Case 3. (× 414.)

c.mm. The red cell appearances were similar to those described in Cases 1 and 2 with well-marked anisocytosis and poikilocytosis (Fig. 1). Many microspherocytes were seen and fragmentation of erythrocytes was a feature, 'broken egg-shell' and triangular forms being prominent. The reticulocyte count was 12%. Heinz bodies were not found in supravitally stained blood films. Blood urea was 260 mg. per 100 ml. There was gross proteinuria and about 200 red cells per high power field were found in the urinary centrifuged deposit. Large numbers of granular, hyaline and waxy casts were also observed. Direct Coombs test was negative. There was no abnormal fragility of red cells and serum electrolytes were normal.

The patient was transfused with 250 ml. blood which raised the haemoglobin level to 12·5 g. per 100 ml. He was maintained on intravenous therapy until all vomiting ceased. Urine output was measured and was adequate. The child was intensely irritable and anorexic for seven days. His blood pressure did not rise excessively—the highest reading was 130/80 mm. Hg on August 29, 1960, and there was a fall to 90/40 mm. Hg in the second and third hospital weeks when the child had made a clinical recovery. On September 1, 1960, his irritability and anorexia ceased quite abruptly, although his blood urea was still 110 mg. per 100 ml.

Throughout his stay in hospital his haemoglobin level never dropped below 10·5 g. per 100 ml. after the initial transfusion, but his platelet count did not become normal until the nineteenth hospital day when the red cell appearances were also normal.

His progress was steady and he was discharged on September 13, 1960, clinically well but with the blood urea still elevated (65 mg. per 100 ml.) and the urine containing a small amount of protein and scanty red cells and casts.

Up to the time of writing the blood urea has remained raised (60 mg. per 100 ml.), but the urine is virtually normal. Clinically the child has thrived and appears to be in excellent health.

Pathological Investigations. These are summarized in Tables 5 and 6. The direct antiglobulin (Coombs) test was negative.

TABLE 5

HAEMOGLOBIN AND TOTAL LEUCOCYTE ESTIMATIONS: CASE 3

Date	Haemoglobin (g./100 ml.)	Platelets per c.mm. (Normal Range 150,000–400,000)	Total Leucocyte Count per c.mm.
25.8.60	5·6	51,000	13,000
27.8.60	12·5	Very scanty	—
29.8.60	12·4	100,000	—
31.8.60	12·2	65,000	6,000
3.9.60	11·0	Very scanty	—
6.9.60	11·0	45,000	7,000
12.9.60	10·5	145,000	10,500
19.9.60	10·8	210,000	—
3.10.60	12·0	Plentiful	12,200
31.10.60	12·8	Plentiful	5,000
15.11.60	12·2	Plentiful	9,900
14.12.60	11·8	Plentiful	11,300

TABLE 6
BIOCHEMICAL INVESTIGATIONS: CASE 3

Date	Serum Sodium (mEq/l.) (Normal Range 141–152)	Serum Potassium (mEq/l.) (Normal Range 4·1–5·6)	Blood Urea (mg./100 ml.) (Normal Range 20–40)	Serum Bilirubin (mg./100 ml.) (Normal Range 0·1–0·8)
25.8.60	142	5·0	260	0·8
31.8.60	142	5·3	110	—
6.9.60			75	
12.9.60			60	
19.9.60			65	
3.10.60			65	
17.10.60			45	
31.10.60			65	
15.11.60			60	
14.12.60			60	

Discussion

There is little doubt that these three patients suffered from anaemia due to haemolysis. Two infants showed frank clinical jaundice, but the other had no evidence of jaundice clinically or in the serum; it is interesting, however, that the skin of Case 1 showed an orange tinge. Presumably the bilirubin was handled sufficiently effectively and rapidly by the liver to prevent the appearance of jaundice.

The microscopical appearances of the peripheral blood films in Cases 1, 2 and 3 were very similar, and the illustration (Fig. 1) is representative of the initial blood picture of all three cases. The films were similar to those illustrated in the articles by Gasser *et al.* (1955), Allison (1957) and Aherne (1957).

Clinically their illnesses closely resembled the cases described by Allison, essentially a haemolytic anaemia with a characteristic blood picture, proteinuria, haematuria and uraemia. Our cases showed the vomiting and pallor which were usual in Allison's cases. Petechial haemorrhages and bruising were not seen in any of his patients nor in two of those reported here, though such haemorrhages were present in one of Aherne's and one of Gasser's cases, and one of the present series. Allison regarded the following laboratory findings as diagnostic. The haemoglobin level was low and the reticulocyte count increased. Peripheral blood films showed, in addition to increased polychromasia, marked fragmentation of erythrocytes and spherocytosis. The platelet count was considerably reduced. The urine contained protein, often in large amounts, and sometimes haemoglobin, erythrocytes and granular casts as well. The blood urea level was usually high.

Most of these features were well illustrated in our cases, but the thrombocytopenia in the first two was not as striking as in Allison's cases.

The types of erythrocytes seen in all the reported cases of this haemolytic-uraemia syndrome, and in these three, have been classified by Dacie (1960) under the heading of 'irregularly contracted erythrocytes' into several different categories. One is the 'burr' cell observed by Schwartz and Motto (1949) and the other is the 'triangular cell' of Dacie, Mollison, Richardson, Selwyn and Shapiro (1953). Dacie (1960) believed that 'burr' and 'triangular' cells were distinct entities, though both types of cell may be present at the same time. 'Burr' cells appear to be artefacts produced on the slide as the cell dries, and are found in a variety of conditions including uraemia. It is doubtful whether their presence denotes increased haemolysis.

'Triangular' cells, on the other hand, are probably always associated with increased haemolysis and may be looked upon as prehaemolytic forms and owe their origin to fragmentation of adult cells *in vivo*. They are found in acute progressive uraemia in adults, in a haemolytic-uraemic syndrome in childhood and in thrombotic thrombocytopenic purpura. The exact pathogenesis of both 'burr' cells and 'triangular' cells is unknown.

The aetiology of the type of haemolytic anaemia associated with uraemia seen in Cases 1, 2 and 3 is unknown. Allison (1957) considered it was a type of thrombotic thrombocytopenia and, at autopsy of his two fatal cases, though nothing abnormal was observed macroscopically, widespread small thrombi in capillaries and arterioles were found microscopically. The thrombi appeared to consist largely of blood platelets and were very numerous in the kidney. In one of the fatal cases described by Gasser *et al.* (1955), the lesions were similar and like those described by Symmers (1952) who considered thrombotic thrombocytopenic purpura to be related to the collagen diseases.

Wile and Sturgeon (1956) reported a similar type of condition in children, and one of their cases was an infant of 10 months. Purpura was, however, a feature of their cases and they ran an acute fulminating course with a fatal outcome. These cases, like adult cases of thrombotic thrombocytopenic purpura, were characterized by haemolytic anaemia, thrombocytopenia and purpura; in addition there were fluctuating neurological disturbances often producing coma and uraemia. Haematuria was always present. Possibly the cases without purpura, described by Allison (1957), Gasser *et al.* (1955) and Aherne (1957), and our Cases 1 and 2, are variants of the same syndrome. The fatal cases of Gasser *et al.* (1955) all showed bilateral cortical necrosis of kidney at autopsy.

One of Allison's cases had neurological signs with

convulsions and a raised cerebrospinal fluid protein, while, of three of Gasser *et al.*'s cases, one had hemiplegia and two had convulsions. All these cases with involvement of the nervous system died. Our Case 1 also had marked neurological disturbance with convulsions, coma and opisthotonus and a raised cerebrospinal fluid protein, and yet she made a complete recovery.

Allison feels that his cases differ from the thrombotic thrombocytopenia which occurs in adults. They occur in children, are not necessarily fatal and there is no purpura. If cases can be kept alive the disease resolves spontaneously in a few days to three weeks. Then haemolysis ceases, haemoglobin concentration rises and platelet counts return to normal. Signs of renal dysfunction disappear, the protein level in the urine and the blood urea fall and the patient makes a complete recovery. No signs of persistent renal damage were found in the cases Allison followed up nor to date in our Cases 1 and 2 (2 years and 16 months respectively); however, Case 3 still shows a blood urea of 60 mg. per 100 ml. four months after the acute illness, and yet this patient showed the speediest clinical response to treatment of all three.

Against the diagnosis of thrombotic thrombocytopenia is the fact that surgical biopsy of skin and muscle taken at the height of the illness in Case 1 showed no platelet thrombi nor was there any evidence of collagen disease, which had been suspected. Yet, in thrombotic thrombocytopenic purpura of adult type, lesions have been numerous in skin and vastus lateralis at autopsy (Symmers, 1952), and this was the site chosen for biopsy in Case 1. Symmers made the diagnosis in one case on the basis of a positive skin biopsy in association with the typical clinical picture. However, on the other hand Blackman, Cohen and Watson (1952) found muscle biopsy of no help in their case, and Wile and Sturgeon (1956) pointed out that a failure to demonstrate the characteristic lesion in biopsy or bone marrow aspiration sections did not necessarily exclude the diagnosis.

Drugs must be considered as possible aetiological agents, but in Case 2 there was no history of exposure nor were Heinz bodies present in any of the cases. However, at the onset of the diarrhoea in Cases 1 and 3 some sulphonamide had been taken. Sixteen months after the illness the blood of Case 1 was found to have a normal glucose-6-phosphate dehydrogenase activity.

Reticuloses, leukaemia, lupus erythematosus and polyarteritis nodosa were excluded by skin biopsy, bone marrow examination and clinical follow-up.

Treatment. Allison felt that his patients responded best to treatment with repeated blood transfusions even to the point of mild 'overtransfusion'. In our first two cases steroid therapy was used in addition on the assumption that, if the pathology was due to widespread platelet thrombi and an underlying vascular lesion, such therapy would be of value. Diamond (1957), commenting on the treatment of thrombotic thrombocytopenic purpura in the *Year Book of Pediatrics*, says: 'Quite possibly early and very large doses of steroid would help carry the patient through the crises which so often lead to death within a few days or weeks . . .'.

It is impossible, with few cases for comparison, to assess the effect of steroid therapy in our patients, but the clinical impression gained was that the disease process was only slightly, if at all, modified. The blood urea remained elevated (three and a half weeks) in Case 1, quite as long as the most severely affected patient in Allison's series, and a second blood transfusion was required 10 days after the onset of therapy. This patient was virtually anuric for five days, the diuresis occurring three days after blood transfusion and institution of high dosage steroid therapy. However, Allison's severe cases of this type died, whereas this baby survived.

In one of Allison's cases where the baby was severely ill for 14 days with marked elevation of the blood urea, blood transfusions were required every few days, a total of seven transfusions being administered in all. In our Case 1, although the haemoglobin level fell, despite the steroid therapy, and although distorted and fragmented erythrocytes remained in the circulation, only two transfusions were required and then with an interval as long as 10 days between them.

Our Case 3, who received no steroid therapy, responded more rapidly from the clinical viewpoint than the other two cases, but continues to have a raised blood urea.

It is interesting to note that all the babies showed some degree of hypertension. This may have been related to steroid therapy in two of them, but Aherne's two cases were also hypertensive, as was our Case 3 (who received no steroids), and hypertension is known to occur in thrombotic thrombocytopenic purpura (Blackman *et al.*, 1952).

Successful treatment with heparin in small doses has recently been reported in a classical case of thrombotic thrombocytopenic purpura in an adult (Bernstock and Hirson, 1960).

Conclusion

It seems probable that these three patients were suffering from the same haemolytic-uraemic syn-

drome. The practical importance of being aware of the existence of the condition is illustrated by the fact that Case 2 was diagnosed by one of us (J.G.) as the result of a telephone conversation with another pathologist, who described the patient as having a haemolytic anaemia with an unusual blood film and a urine 'suggestive of acute nephritis'. In addition, Case 3 was diagnosed by one of us (K.G.I.) during the performance of a routine blood count from the red cell appearances and the accompanying thrombocytopenia. These suggested that the blood urea would be raised and that the urine examination would be abnormal, which they both proved to be.

It is necessary, therefore, for both clinician and pathologist to be acquainted with this syndrome.

Summary

Three cases of haemolytic anaemia with characteristic erythrocyte morphology, uraemia, proteinuria, haematuria and thrombocytopenia are described. and differential diagnosis and treatment are discussed.

Two infants recovered after treatment with blood transfusions and steroids, and one infant treated with blood transfusions but without steroids made a clinical recovery, although his blood urea remained high four months after the acute illness.

It is of practical importance for both clinician and pathologist to be acquainted with this apparently little-recognized syndrome.

We wish to thank the Director of the South African Institute for Medical Research and staff members; and Dr. Barbara Wallace of the S.A.I.M.R. laboratory, Welkom, Orange Free State, for making available the results of certain pathological investigations. We are also indebted to Mr. M. Ulrich, of the S.A.I.M.R., Johannesburg, for the photograph, and to Dr. R. W. Charlton of the Medicine Department, University of the Witwatersrand, for the determination of the glucose-6-phosphate dehydrogenase activity.

References

Aherne, W. A. (1957). The 'Burr' red cell and azotaemia. *J. clin. Path.*, **10**, 252.

Allison, A. C. (1957). Acute haemolytic anaemia with distortion and fragmentation of erythrocytes in children. *Brit. J. Haemat.*, **3**, 1.

Bernstock, L. and Hirson, C. (1960). Thrombotic thrombocytopenic purpura. Remission on treatment with heparin. *Lancet*, **1**, 28.

Blackman, N. S., Cohen, B. M. and Watson, J. (1952). Thrombotic thrombopenic purpura; report of case. *J. Amer. med. Ass.*, **148**, 546.

Dacie, J. V. (1960). *The Haemolytic Anaemias—Congenital and Acquired*, Part 1, 2nd ed. Churchill, London.

——, Mollison, P. L., Richardson, N., Selwyn, J. G. and Shapiro, L. (1953). Atypical congenital haemolytic anaemia. *Quart. J. Med.*, **22** (n.s.), 79.

Diamond, L. K. (1957). Editorial comment, in the *Yearbook of Pediatrics* (1957-58 Year Book series), ed. S. S. Gellis, p. 290. The Year Book Publishers, Chicago.

Gasser, C., Gautier, E., Steck, A., Siebenmann, R. E. and Oechslin, R. (1955). Hämolytisch-urämische Syndrome: Bilaterale Nierenrindennekrosen bei akuten erworbenen hämolytischen Anämien. *Schweiz. med. Wschr.*, **85**, 905.

Schwartz, S. O. and Motto, S. A. (1949). The diagnostic significance of 'Burr' red blood cells. *Amer. J. med. Sci.*, **218**, 563.

Symmers, W. St. C. (1952). Thrombotic microangiopathic haemolytic anaemia (thrombotic microangiopathy). *Brit. med. J.*, **2**, 897.

Wile, S. A. and Sturgeon, P. (1956). Thrombotic thrombocytopenic purpura. Review of the subject with a report of three cases in children. *Pediatrics*, **17**, 882.

FOETAL HAEMOGLOBIN IN HAEMOLYTIC DISEASE OF THE NEWBORN

BY

THOMAS E. OPPÉ* and IAN D. FRASER

From the Departments of Child Health and Pathology, University of Bristol and Southmead General Hospital, Bristol

(RECEIVED FOR PUBLICATION MARCH 3, 1961)

A difference in the proportions of foetal (Hb-F) and adult (Hb-A) haemoglobins between normal infants and those affected by haemolytic disease due to the rhesus factor was first reported by Jonxis (1948). His work was later extended by several investigators and the differences were confirmed. The hitherto reported studies have been concerned mainly with full-term infants and it was the purpose of the present investigation to gain information about the proportions of Hb-F and Hb-A in affected infants born prematurely. As a result we are able to present some original data concerning the problem and to offer an explanation of the results obtained which differs from those previously suggested.

Material and Methods

Cord blood samples were obtained at delivery from 37 infants affected by haemolytic disease due to the rhesus factor. Cord blood samples were also taken from 29 infants of similar maturities but not affected by haemolytic disease.

The samples were analysed for total haemoglobin concentration by the Medical Research Council grey wedge photometry and for Hb-F by the alkali-denaturation method of Singer, Chernoff and Singer (1951).

Maturity was assessed clinically and although birth weight was an important factor in assessment the cases were grouped according to the estimated gestational age. Cases delivered during the 35th to 36th week of pregnancy (10 cases) were termed 'premature', during the 37th to 38th week (15 cases) 'pre-term' and after the 38th week (12 cases) 'full-term'.

The severity of the haemolytic disease was assessed largely on the cord blood haemoglobin value. A total haemoglobin of 100% (14·8 g./100 ml.) or above placed the infant as 'mildly' affected; if the cord haemoglobin value was 78% (11·5 g./100 ml.) or below the infant was assessed as 'severely' affected. A classification of 'moderate' disease was made if the haemoglobin was between these levels. Clinical condition of the baby, maternal antibody titre and subsequent progress entered into the evaluation of the babies, but in this series did not cause any major deviation from assessments of severity based on cord haemoglobin level.

Premature induction of labour was performed for clinical reasons and broadly followed the indications recommended by Tovey and Valaes (1959), the clinician in charge of the case making the decision without knowledge of this study.

Results

Fig. 1 shows the individual values for percentage Hb-F in the cord blood of the affected infants related to gestational age and severity of haemolytic disease. For comparison the means ±2 standard deviations of similar determinations on normal infants are also shown. It can be seen that with the exception of mildly affected infants at term, the percentage of Hb-F in the affected infants falls well below the expected value at all periods of gestation.

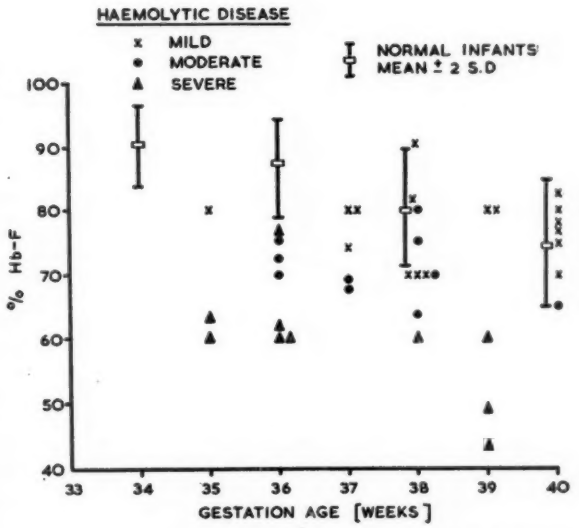


FIG. 1.—The results of individual determinations of percentage foetal haemoglobin in 37 infants affected with haemolytic disease compared with mean values of percentage foetal haemoglobin in normal infants.

* Present address: St, Mary's Hospital Medical School, London, W.2.

TABLE 1

	No. of Cases	Mean % Hb-F	Standard Deviation	S.E. of Mean
Mild	17	77·9	6·19	1·50
Moderate ..	10	71·0	4·85	1·53
Severe	10	59·8	8·20	2·59

The mean values for percentage foetal haemoglobin in the affected infants grouped by severity of disease but ignoring gestational age are given in Table 1.

The difference between these means by analysis of variance is significant at $p = 0{\cdot}001$ level. A 't' test between the means of the mild and moderate cases gave $t = 3{\cdot}20$ ($p = 0{\cdot}01$). If gestational age were taken into account the significance would be even higher as the severer cases were more immature than the mild cases.

The reported findings that infants affected by erythroblastosis have a proportionate increase in Hb-A is confirmed and, furthermore, it is apparent that this increase is present by the 36th week and is correlated with severity of disease.

However, the demonstration of a proportionate increase of Hb-A does not show whether it is due to an absolute increase in the amount of Hb-A or a diminished quantity of Hb-F. In Fig. 2 it is made clear that in part at least the proportionate increase in Hb-A is due to an absolute increase in concentration of adult haemoglobin. There the total haemoglobin concentration in grammes per cent. is plotted with the absolute contributions made by the two varieties of haemoglobin. The cases are grouped by estimated gestational age and by severity of disease.

The data from the premature infants (35-36 weeks) are the most instructive and normal infants are compared with affected infants irrespective of severity in Table 2.

TABLE 2

	No.	Mean Hb-A (g. %)	Standard Deviation
Normal	9	1·94	±0·678
Affected	10	3·48	±0·557

A t test between these means gives a value of $t = 5{\cdot}42$ ($p = 0{\cdot}001$). It is clear that the reduction in total haemoglobin caused by the haemolytic disease affects the Hb-F fraction and there is a significantly greater absolute concentration of Hb-A in the peripheral blood of affected infants than in normal premature infants.

A further analysis of the data is instructive. The absolute concentrations of Hb-F and Hb-A in the cord blood samples can be plotted against the individual total cord blood haemoglobin values. For convenience these two analyses are placed on the same graph in Fig. 3. It can be seen that there is a linear correlation between cord blood total haemoglobin and Hb-F, and a much less marked correlation with Hb-A.

The correlation coefficients were calculated and gave:

(*a*) total haemoglobin v Hb-F, $r=0{\cdot}968$, $p=0{\cdot}001$;
(*b*) total haemoglobin v Hb-A, $r=0{\cdot}365$, $p=0{\cdot}05$.

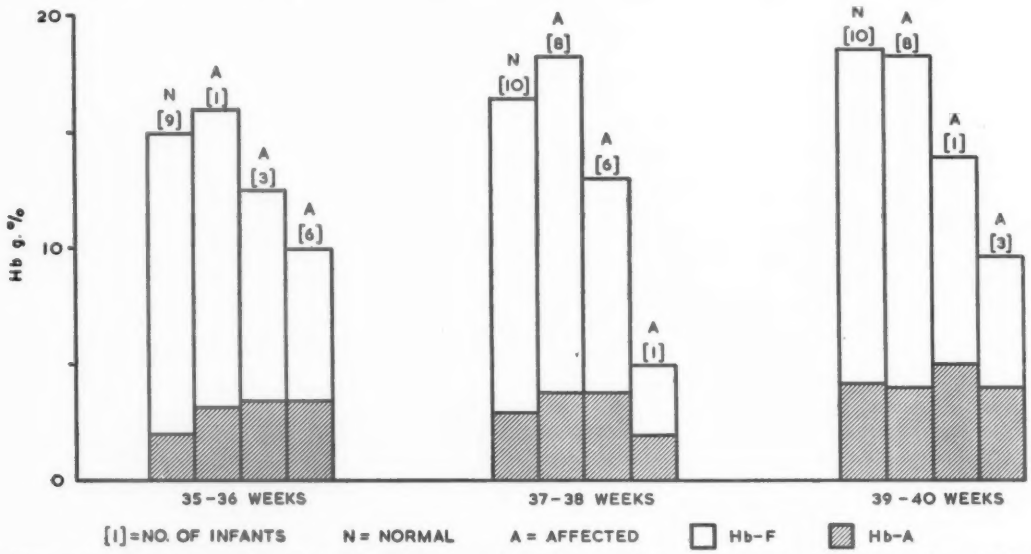


FIG. 2.—Mean values for concentration of total haemoglobin and fractions of adult and foetal haemoglobin in the cord blood of premature, pre-term and full-term infants. At each gestational age unaffected infants are represented by the left-hand columns.

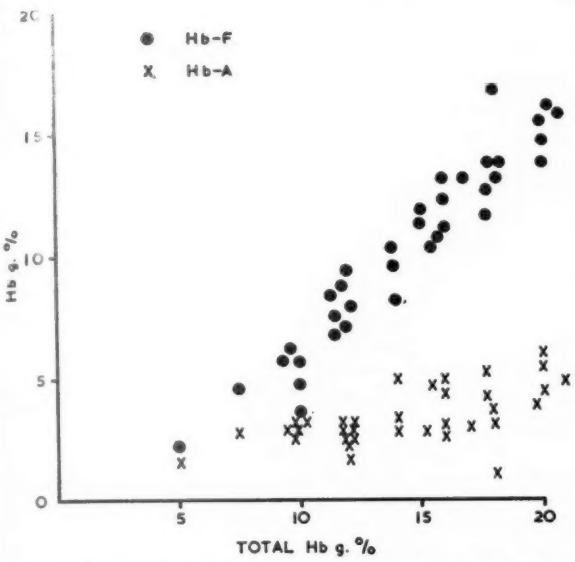


FIG. 3.—Concentration of total haemoglobin in affected infants compared with the fractions of foetal haemoglobin and of adult haemoglobin.

Discussion

The results presented confirm the finding that in haemolytic disease there is an increase in the proportion of adult haemoglobin (Hb-A) in the peripheral blood and that this proportionate increase of Hb-A is due to a decrease in the concentration of foetal haemoglobin (Hb-F). We have shown further that these differences in haemoglobin constitution are apparent in affected infants born during the 35th to 36th weeks of gestation as well as nearer or at full-term. In our material there are significant correlations between the severity of the haemolytic disease (as estimated by anaemia at birth) and increase in percentage Hb-A; and between the total haemoglobin concentration and concentration of the Hb-F fraction. There is a somewhat less significant correlation between the total haemoglobin concentration and the Hb-A fraction. In these respects our results are essentially similar to those of Schulman and Smith (1954) and Brody and Engström (1960). However, in confirming Schulman and Smith's (1954) finding that in haemolytic disease there is an absolute increase in the concentration of Hb-A we are at variance with Brody and Engström (1960). It is of considerable interest that we found this to be so even in premature infants.

These discrepancies are more likely to be due to differences in the cases examined than variations in technique, because there is good agreement between investigators regarding other aspects of the same data. They are, however, important because much of the discussion regarding the interpretation of the changes found in haemolytic disease depends upon the controversial findings. Briefly it is maintained by Schulman and Smith (1954) that evidence of an increase in concentration of Hb-A indicates a preferential generation of Hb-A in the foetus under stress, while Brody and Engström (1960) on their data prefer to revert to the original hypothesis of Jonxis (1948) that there is selective destruction of cells containing Hb-F.

In our view the experimental data can be reasonably explained without recourse to either preferential generation of one form of haemoglobin or selective destruction of the other, and the contradictions can be reconciled by biological variations within the spectrum of the disease process. If it is assumed that in haemolytic disease of the newborn there is random destruction of vulnerable erythrocytes (Mollison, 1943), and that during the latter weeks of pregnancy there is a constantly increasing synthesis of Hb-A from a small fraction of the total haemoglobin synthesis at 34 weeks to a large proportion at term (Walker and Turnbull, 1955; Cook, Brodie and Allen, 1957; Brody and Nilsson, 1960; Beaven, Ellis and White, 1960), it is possible to construct a simple arithmetical model of the dynamics of haemoglobin formation at this time. The result of such an artificial construction in terms of haemoglobin differentiation in the peripheral blood is graphically illustrated in Figs. 4 and 5.

'Foetus A' (Fig. 4) represents a normal foetus during the last 10 weeks of gestation, in which the haemoglobin mass triples in volume and the synthesis of adult haemoglobin increases regularly from 10% of the total at 31 weeks to 70% at term. The assumed erythrocyte life is 100 days. It can be

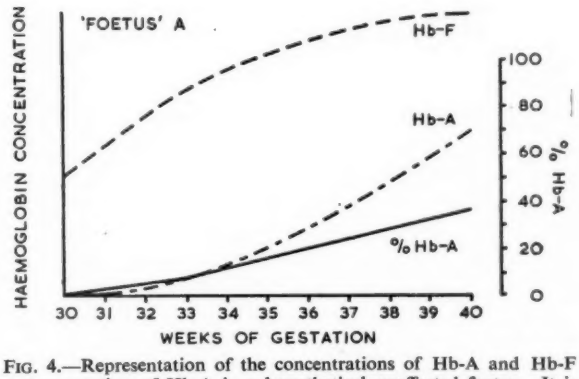


FIG. 4.—Representation of the concentrations of Hb-A and Hb-F and proportion of Hb-A in a hypothetical unaffected foetus. It is assumed that during the last 10 weeks of gestation the haemoglobin mass triples in volume and that the survival time of the foetal erythrocyte is 100 days. A constant increment in the synthesis of Hb-A is assumed.

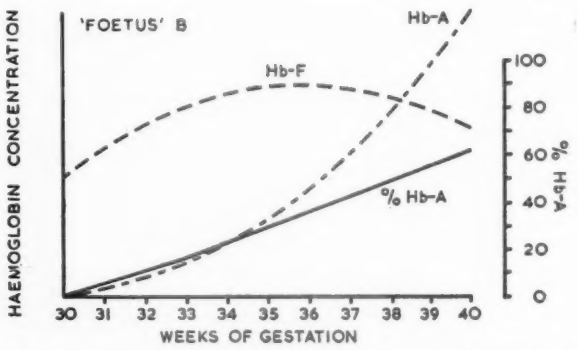


FIG. 5.—Representation of the concentrations of Hb-A and Hb-F and the proportion of Hb-A in a hypothetical affected foetus. It is assumed that during the last 10 weeks of gestation the haemoglobin mass triples in volume and that the survival time of the foetal erythrocyte is 20 days with a constant increment in the synthesis of Hb-A, similar to that in 'foetus' A (Fig. 4).

seen that the proportion of Hb-A rises steadily as does the concentration of Hb-A, whereas the concentration of Hb-F rises only slowly after the 36th week. This, in spite of the artificial linearity, is representative of the known facts in normal infants. 'Foetus B' (Fig. 5) represents an affected infant over the same time period and with the same rate of growth and synthesis of Hb-A. However, the assumed erythrocyte life is 20 days and it is further assumed that the red cells are destroyed randomly. Comparison of the two figures shows that the calculated 'affected' baby displays the same differences in haemoglobin differentiation as are found between normal and erythroblastotic infants.

This simple representation of the dynamics does not take into account the failure of the severely affected baby to produce adequate haemoglobin to maintain growth and compensate for haemolysis. It is probably the relationship between the erythropoietic capacity of the baby and the variation in survival time of the red cells combined with variation in rates of Hb-A synthesis which complicate interpretation of the experimental data and account for the discrepancies found.

Until further more direct measurements of the variables involved are available it seems reasonable to interpret the differences in foetal and adult haemoglobins in haemolytic disease as due to the effects of random haemolysis and blood regeneration occurring at a time when there is a normal increase in the synthesis of adult haemoglobin. It seems unnecessary to propound either a selective destruction of cells containing predominantly Hb-F or to suggest that stress on the erythropoietic organ induces preferential synthesis of adult haemoglobin.

Summary

Determination of foetal haemoglobin in the cord blood samples of 37 infants suffering from haemolytic disease and comparing them with normal infants of similar gestational age has shown the following:

(1) An increased proportion of Hb-A in the affected infants which is related to the severity of the disease.
(2) A decrease in the concentration of Hb-F which is related to the total haemoglobin concentration.
(3) An increase in the concentration of Hb-A which is poorly correlated with total haemoglobin concentrations.
(4) These effects are present from the 35th week of gestation.

An explanation of these findings is offered suggesting that they are the expected results of haemolysis and increased erythropoiesis at a time when there is regularly increasing biosynthesis of the Hb-A fraction.

We are grateful to the obstetricians and paediatricians at Southmead General Hospital for permission to investigate their cases. This study was part of a wider investigation of haemolytic disease undertaken in co-operation with Dr. G. H. Tovey, Director of the S.W. Region Blood Transfusion Service, and we are grateful for his help and advice. The statistical analyses were performed by Miss E. M. Duncan of the Bristol Health Department. We also thank Professor A. V. Neale and Dr. A. B. Raper for their encouragement and Dr. P. L. Mollison for his advice in interpretation of the data.

REFERENCES

Beaven, G. H., Ellis, M. J. and White, J. C. (1960). Studies on human foetal haemoglobin. II. Foetal haemoglobin levels in healthy children and adults and in certain haematological disorders. *Brit. J. Haemat.*, **6**, 201.

Brody, S. and Engström, L. (1960). Foetal and adult haemoglobin in newborn infants with erythroblastosis foetalis. *Acta paediat., Stockh.*, **49**, 868.

—— and Nilsson, B. A. (1960). Foetal and adult haemoglobin mass in relation to foetal development. *J. Obstet. Gynaec. Brit. Emp.*, **67**, 827.

Cook, C. D., Brodie, H. R. and Allen, D. W. (1957). Measurement of fetal hemoglobin in newborn infants. Correlation with gestational age and intrauterine hypoxia. *Pediatrics*, **20**, 272.

Jonxis, J. H. P. (1948). Foetal haemoglobin and erythroblastosis. *Nature (Lond.)*, **161**, 850.

Mollison, P. L. (1943). The survival of transfused erythrocytes in haemolytic disease of the newborn. *Arch. Dis. Childh.*, **18**, 161.

Schulman, I. and Smith, C. H. (1954). Fetal and adult hemoglobins in hemolytic disease of the newborn. *Amer. J. Dis. Child.*, **87**, 167.

Singer, K., Chernoff, A. I. and Singer, L. (1951). Studies on abnormal hemoglobins. I. Their demonstration in sickle cell anemia and other hematologic disorders by means of alkali denaturation. *Blood*, **6**, 413.

Tovey, G. H. and Valaes, T. (1959). Prevention of stillbirth in Rh haemolytic disease. *Lancet*, **2**, 521.

Walker, J. and Turnbull, E. P. N. (1955). Haemoglobin and red cells in the human foetus. III. Foetal and adult haemoglobin. *Arch. Dis. Childh.*, **30**, 111.

INFANTILE CONGENITAL ANEUTROCYTOSIS

BY

DAGFINN AARSKOG

From the School of Medicine, Paediatric Department, University of Bergen, Norway

(RECEIVED FOR PUBLICATION MARCH 22, 1961)

In 1956 Kostmann reported a new disease of infancy which he termed 'infantile genetic agranulocytosis'. He described 14 children of both sexes in nine families. All but two of the children died as a result of the disease. For six of them detailed clinical and histological data were reported. The disease occurs during early infancy with infections particularly of the skin. There is a complete or almost complete lack of polymorphonuclear neutrophil leucocytes in the peripheral blood, and the bone marrow shows a marked retardation or block in the maturation of the myelopoietic cells. All of the affected children in his report lived in the northern part of Sweden. Close consanguinity between the parents was established in five of the nine families. Kostmann presented a genetic analysis which supported the conclusion that the disease was primarily caused by a single recessive autosomal gene (a simple recessive mutation).

Since Kostmann's original report three additional cases belonging to the same families have been examined (Kostmann, 1960).

Hedenberg (1959) described a case of agranulocytosis discovered in a girl at the age of 1 week. He found good agreement with infantile genetic agranulocytosis. In his case there was no consanguinity between the parents. The family lived in the southern part of Sweden, and there was no relationship to the families described by Kostmann.

Outside Sweden, Luhby, Speer, Lee and Shapiro (1957) described an infant who presented with agranulocytosis at 2 weeks of age; it persisted until the child died of an overwhelming infection when 7 months old. The authors concluded that the case represented a congenital genetic agranulocytosis due to an inborn error of development and maturation of the neutrophils. They found the condition apparently identical to that described by Kostmann. Kinsker and Panos (1957) studied two infants aged 7 and 30 months, both of whom had fatal agranulocytosis. They stated that the clinical, laboratory and pathological features closely fitted the syndrome described by Kostmann. However, all cases on record outside those belonging to the families reported by Kostmann have failed to show hereditary or genetic factors.

The number of reported cases of this syndrome is still small, although this deleterious mutation seems now to occur in different areas. The purpose of this paper is to present a further case with typical clinical and laboratory findings.

Case Report

The patient was a 2-month-old girl admitted to the Children's Hospital, Bergen, on June 4, 1960, because of jaundice, pyodermia and otitis.

There was no consanguinity between the parents, and the patient was the fourth child. A sister died of meningitis at the age of 2 months. There was no known case of blood disorder in the family.

The mother did not use any medicaments during the pregnancy which was uneventful. The delivery was spontaneous at term on April 4, 1960, and the child's birth weight was 2,870 g.

At the age of 1 week she developed pyodermia, and when 10 days old a slight jaundice was observed. At the age of 6 weeks she had an otitis and was treated with aureomycin, 120 mg. daily.

Upon admission to the Children's Hospital she looked ill, but her general condition was not severely affected. She was thin, pale and slightly icteric. Temperature 37·7° C. On the abdomen she had several pea-sized, bluish-red infiltrations. The liver was felt about 2 cm. below the right costal margin and the spleen just below the left. She had signs of an otitis with a clear, viscoid discharge. The blood examinations are summarized in Table 1. Examination of the bone marrow by needle aspiration revealed a cellular marrow with a striking absence of neutrophilic myeloid elements (Table 2). The total serum protein was 6 g. per 100 ml. with decreased albumin fraction and elevated gamma-globulin level. Examination of the serum for leucocyte antibodies was negative.

A blood culture was negative. Cultures from the ear revealed coagulase positive *Staphylococcus aureus*, and from the cutaneous infiltrations there was growth of *Escherichia coli*, *Proteus vulgaris* and *Enterococcus*.

She was treated with large doses of penicillin and with streptomycin, erythromycin, chloramphenicol and

TABLE 1
BLOOD EXAMINATIONS

Date (1960)	Hb (%)	R.B.C. (million/ mm.^{3})	W.B.C. (per mm.^{3})	Stab Cells (%)	Polymorphonuclear Neutrophils (%)	Eosinophils (%)	Basophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets (per mm.^{3} × 10^3)	Reticulocytes (per 1,000)	Sedimentation Rate
4/6	62	4·01	13,300	—	—	2	—	46	52	92	24	1·5
6/6			20,800	—	—	1·5	0·5	63	31			
13/6	48	2·92	17,800	0·5	0·5	4·5		82	12·5	170		·0
13/6	Blood transfusion											
20/6	71	3·82	14,700	—	—	9·5	1	41·5	48	142	52	
27/6	69	3·36	18,700	—	—	8·5	0·5	77	14		12	1·6
4/7	68	3·38	11,800	—	—	3	1	77	19		10	
7/7											54	
9/7			16,200	—	—	9·5		52·5	38			
23/7	Blood transfusion											
27/7	78									315		
29/7	65	3·82	30,800	—	—	2	0·5	63·5	34		28	
8/8	65	3·80	15,300	—	—	12	1	52	35	248	30	
15/8	63	3·53	36,100	—	—	8	1	50·5	40·5		36	
29/8	Blood transfusion											
9/9	85	4·87	23,800	—	—	9·5		41	49·5		12	
14/9	Blood transfusion											
15/9	87	4·82	18,000	—	—	8·5		66	25·5		6	
19/9			18,000	—	—	2	0·5	72	25·5			

vancomycin in appropriate doses. She also received repeated blood transfusions. However, the clinical course was marked by intermittent fever and a new outbreak of cutaneous infiltrations. Smears of the latter showed the cellular reaction to be monocytic and lymphoid. Throughout the whole course only occasional neutrophilic granulocytes were found in smears from the peripheral blood. Platelet and reticulocyte counts were within normal limits (Table 1). Attempts to improve the bone marrow with vitamin B_{12} and folic acid were of no effect.

On August 30, 1960, physical examination revealed signs of pneumonia, and a radiograph showed massive consolidations in both lungs. Despite massive antibiotic therapy she died on September 19, 1960, of an overwhelming lung infection.

TABLE 2
BONE MARROW EXAMINATION*

Blood basophils		0·8
Basophilic myelocytes	0·6	
Segmented basophils	0·2	
Eosinophils		9·8
Eosinophilic myelocytes	3·0	
Eosinophilic metamyelocytes	1·6	
Stab eosinophils	5·2	
Neutrophils		0·8
Neutrophilic promyelocytes II	0·8	
Monocytes		26·8
Monoblasts	0·4	
Promonocytes	3·4	
Monocytes	22·8	
Athrophagocytes	0·2	
Lymphocytes		44·8
Plasma cells		17·0
Plasmoblasts	1·2	
Proplasmocytes	9·2	
Plasmocytes	6·6	
Megakaryocyte-platelet system		0·4
Megakaryocytes	0·4	
Normocytes		8·0
Basophilic normoblasts	1·6	
Polychromatophilic normoblasts	3·0	
Oxyphilic normoblasts I	2·4	
Oxyphilic normoblasts II	1·0	
Non-haemopoietic cells		0·4
Osteoblasts	0·4	

* Examination carried out on August 8, 1960 (500 cells were counted).

Autopsy. At autopsy scattered pleural adhesions were found. In the right lung there were two large abscesses, and in the left lung several bronchopneumonic foci. Microscopically the wall of the lung abscesses was infiltrated by mononuclear cells with many plasma cells. The spleen was also rich in plasma cells and contained large amounts of haemosiderin. The bone marrow showed pronounced myelofibrosis with deposits of haemosiderin. It contained many eosinophilic granulocytes and plasma cells. In the kidneys there were scattered foci of cellular infiltrations containing mainly lymphoid cells, but also many plasma cells and some eosinophilic granulocytes.

Definite polymorphonuclear neutrophilic leucocytes were not found.

Discussion

Agranulocytosis after drug therapy is a well-known feature in adults, and is also known as a rare complication in infancy and childhood. The present patient did not receive medicaments known to cause agranulocytosis, neither did the mother use any drug during the pregnancy.

It is also a well-known clinical fact that severe infections, especially sepsis, may be associated with

leucopenia and a relative granulocytopenia. However, leucopenia is not a common feature in sepsis. Recently Nyhan and Fousek (1958) reported a series of 106 newborn infants with sepsis. Leucopenia was noted in five infants. Persistent absence of polymorphonuclear neutrophil leucocytes similar to that observed in this patient hardly occurs in sepsis.

During the past few decades a number of other conditions occurring in infancy and childhood have been observed in which there is an isolated reduction or complete absence of polymorphonuclear neutrophil leucocytes. Transitory granulocytopenia of the newborn was described by Slobody, Abramson and Loizeaux (1950) and Lehndorff (1951). In this condition there is a pronounced granulocytopenia with a duration of several days up to four weeks. During the granulocytopenic phase there is a pattern of maturation arrest at the neutrophil myelocyte stage in the bone marrow. The persistent nature of the aneutrocytosis in the present case rules out this possibility.

Chronic granulocytopenia in children was first described by Fanconi (1941), but Salomonsen (1948) first put forward the opinion that the syndrome represented a distinct clinical entity. Stahlie (1956) reported a case and collected 15 cases from the literature. The syndrome is characterized by a chronic, marked, selective granulocytopenia with a corresponding leucopenia. The bone marrow is normal. The disease usually starts after the age of 6 months, runs a benign protracted course with a tendency to infections and spontaneous cure. This clinical entity differs from the case reported in the patient's age at onset, the pathological bone marrow, the grave course and fatal outcome.

The present case seems to correspond closely with Kostmann's syndrome. However, there was no consanguinity between the parents and to date no other conclusive case of the disease has been found in the family. It is noteworthy that the patient had a sister who died of meningitis at the age of 2 months. Unfortunately her blood was not examined. The early onset in the neonatal period with skin manifestations, the relentless clinical course as well as the findings in the peripheral blood and bone marrow are in good agreement with the findings in Kostmann's cases.

The monocytosis accompanying the aneutrocytosis in the patient resembles that seen in several previously reported cases. In two of Kostmann's cases the monocytes made up 50% of the total number of white cells. Monocytosis of moderate degree was also observed in another case. A moderate increase in the total number of monocytes was noted in the case reported by Luhby *et al.* (1957). Hedenberg also noted monocytosis, and in his case a varying connexion between the infections and monocytosis could be observed. Tobler and Buser-Plüss (1942) demonstrated experimentally that the monocytes in a patient with agranulocytosis had a considerably stronger phagocytic function than those of controls. The monocytosis may therefore represent a compensatory mechanism for the impaired phagocytic function in this patient. The elevated serum gamma-globulin level found in the present patient may also be compensatory as an attempt to raise the immunobiological protective mechanisms against infection. Hypergammaglobulinaemia was also noted by Kostmann in one case and was marked in both cases reported by Kniker and Panos (1957). The latter authors also found eosinophilia and plasmocytosis in the bone marrow, findings similar to those in the present patient. In view of the role played by plasma and eosinophilic cells in the immunobiological response to infection, it seems justifiable to look upon the plasmocytosis and eosinophilia also as secondary phenomena.

Considering the terminology of this syndrome it seems more reasonable to use the term aneutrocytosis than agranulocytosis, since only the polymorphonuclear neutrophilic leucocytes are affected. The eosinophilic and basophilic leucocytes may actually be increased.

Summary

A case of infantile congenital aneutrocytosis is presented. A 2-month-old girl who suffered from infections starting soon after birth, revealed an almost complete absence of neutrophilic myelogenous elements in the peripheral blood and bone marrow. This persisted until she died at the age of 5 months of an overwhelming pulmonary infection. The case seemed to correspond closely with Kostmann's syndrome, but there was no evidence of genetic background.

I am indebted to Ehrendozent Dr. med. E. Undritz, Basel, Switzerland, for examining the bone marrow smear, and to Dr. P. Lexow, University of Bergen, for the post-mortem examination. I wish to express my appreciation to Prof. A. Sundal and to Dr. O. K. Harlem for their valuable help and criticism.

REFERENCES

Fanconi, G. (1941). Klinische Demonstrationen. *Ann. paediat. (Basel)*, **157**, 317.

Hedenberg, F. (1959). Infantile agranulocytosis of probably congenital origin. *Acta paediat. (Uppsala)*, **48**, 77.

Kniker, W. T. and Panos, T. C. (1957). Idiopathic infantile agranulocytosis with hypergammaglobulinemia. *A.M.A. J. Dis. Child.*, **94**, 549.

Kostmann, R. (1956). Infantile genetic agranulocytosis. *Acta paediat.* (*Uppsala*) **45**, suppl. 105.

—— (1960). Personal communication.

Lehndorff, H. (1951). Transitorische Granulocytopenie beim Neugeborenen. *Helv. paediat. Acta*, **6**, 173.

Luhby, A. L., Speer, F. D., Lee, R. and Shapiro, A. D. (1957). Congenital genetic agranulocytosis. *A.M.A. J. Dis. Child.*, **94**, 552.

Nyhan, W. L. and Fousek, M. D. (1958). Septicemia of the newborn. *Pediatrics*, **22**, 268.

Salomonsen, L. (1948). Granulocytopenia in children. *Acta paediat.* (*Uppsala*), **35**, 189.

Slobody, L. B., Abramson, H. and Loizeaux, L. S., Jr. (1950). Agranulocytosis in the newborn infant. *J. Amer. med Ass.*, **142**, 25.

Stahlie, T. D. (1956). Chronic benign neutropenia in infancy and early childhood. Report of a case with a review of the literature. *J. Pediat.*, **48**, 710.

Tobler, W. and Buser-Plüss, E. (1942). Beobachtungen in einem Falle von chronischer, myelogener, hochgradiger Neutropenie mit monocytärer Reaktion. *Ann. paediat.* (*Basel*), **159**, 58.

A LONGITUDINAL STUDY OF THE GROWTH AND DEVELOPMENT OF PREMATURELY AND MATURELY BORN CHILDREN

PART VIII: MORBIDITY IN THE AGE PERIOD 2–5 YEARS

BY

CECIL MARY DRILLIEN

From the Department of Child Life and Health, University of Edinburgh

(RECEIVED FOR PUBLICATION FEBRUARY 16, 1961)

This paper, which is the eighth in a series presenting findings in a long-term study of growth and development in a sample of children of different birth weight, describes the health history of the group from 2 to 5 years. A description of the sample and methods of investigation is given elsewhere (Drillien, 1958).

All children were visited within one month of their third, fourth and fifth birthdays.

An illness is here defined as a disease incident normally necessitating medical attention or hospital admission. In the analysis of morbidity in the first two years of life (Drillien, 1959a), it was noted that some mothers, particularly middle-class women with first babies, called the doctor for trivial ailments and these were excluded from the analysis. After the age of 2 years, very few mothers requested medical attention without reasonable cause, although, as in the first two years, many poor working-class mothers ignored illness which would have received attention in better homes. In particular, sore throats, enlarged adenoids with persistent nasal discharge, and recurrent otitis media with discharge, went untreated in these homes. In addition, it was obvious that the accuracy of recall decreased with declining social standards. Because of this, social class differences in incidence of illness found in the subsequent analysis are likely to be smaller than the real differences which exist.

Of the 595 children enrolled in the survey, a full health history up to the age of 5 years was recorded for 514 (86%). The social class distribution of those lost from the survey does not differ significantly from that of those remaining at 5 years.

Patterns of Morbidity in the First Five Years

Fig. 1 illustrates the relative amount of medical illness suffered by premature and maturely born children in the first five years of life divided into five sections: respiratory disease, infections of ear, nose and throat; gastro-intestinal infections, specific fevers; and all other causes.

The incidence of respiratory infection which accounted for one-half of all medical illness in the first two years, showed a marked decline in the third year, and a lesser decline in the next two years. Conversely, the incidence of infections of ear, nose and throat increased steadily with age and in the fifth year of life accounted for about one-third of all recorded illness.

The incidence of specific fevers reached a maxi-

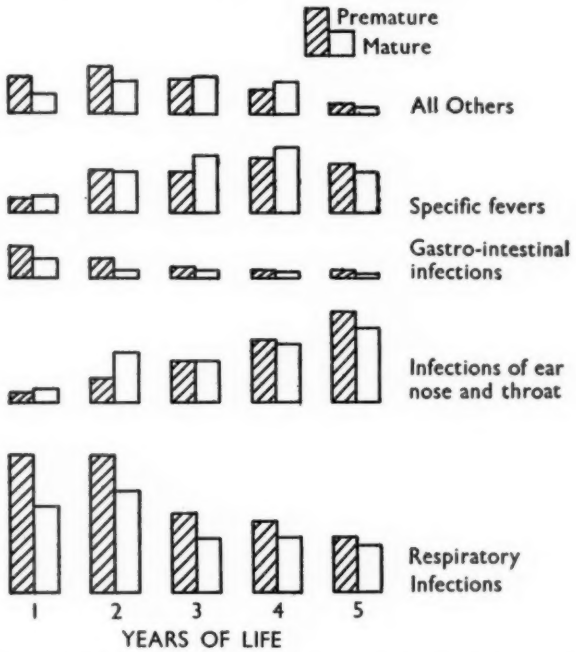


FIG. 1.—Relative morbidity in first five years of life by diagnostic category for premature and maturely born children.

mum between 3 and 4 years. The overall incidence of illness at all ages up to 5 was higher in the prematurely born, but after the age of 2 years differences in morbidity were due mainly to the lower average social class of the prematurely born. Below this age there appeared to be a real excess of respiratory illness in prematurely born children, especially boys.

Respiratory Disease

In the third, fourth and fifth years of life respiratory illness accounted for 34, 30 and 21% of total medical illnesses. As in the first two years a social gradient was found in the number and severity of respiratory infections. Using the scoring method described in a previous paper (Drillien, 1959b), the amount of respiratory disease suffered by children in homes where maternal efficiency was graded 3 and 4 (fair and poor) was between three and four times as high as that found in children where maternal efficiency was graded 1 and 2 (very good and good) in the first two years. In the third, fourth and fifth years of life this ratio was roughly one and a half to one.

Effect of Repeated Respiratory Illness in First Two Years. In the first two years, 39 children were reported as having repeated 'chesty colds', bronchitis and pneumonia. Of these, 33 were followed up to 5 years and two more to 4 years. Twenty-four of the 39 children came from homes where maternal efficiency was graded fair or poor. After the age of 2, only four of the 35 children followed to 4 years had a marked excess of lower respiratory infections as compared with children from similar homes, but without this early history. The incidence of bronchitis and pneumonia complicating measles or whooping cough contracted after the age of 2 was no higher in these children than would be expected when maternal efficiency was taken into account.

Asthma. In the age period 2 to 5 years, 13 children suffered from recurrent attacks of wheezy breathing, dyspnoea and cough which were diagnosed as asthma, of which only one case presented the typical picture of an allergic asthma. Five of the 13 children had had recurrent lower respiratory infections from infancy, with an asthmatic type of breathing developing after the age of 2 years. These later attacks were always associated with an upper respiratory infection. Four children developed asthmatic bronchitis after the age of 2 years. One child developed recurrent asthmatic attacks after being in hospital, but the condition cleared without treatment in three months. She had previously reacted to maternal separation by unexplained vomiting. Four of the 13 children had quite severe infantile eczema before or during the same period as the asthmatic attacks. Of seven other children with a history of severe or prolonged infantile eczema, five also suffered from recurrent lower respiratory infections in the first two years of life, but without any obvious features of asthma.

In eight further cases of milder infantile eczema, consisting of dry scaly patches over scalp, forehead, cheeks, upper chest or back, lasting for 12 months, there was no history of excessive susceptibility to lower respiratory infection at any age.

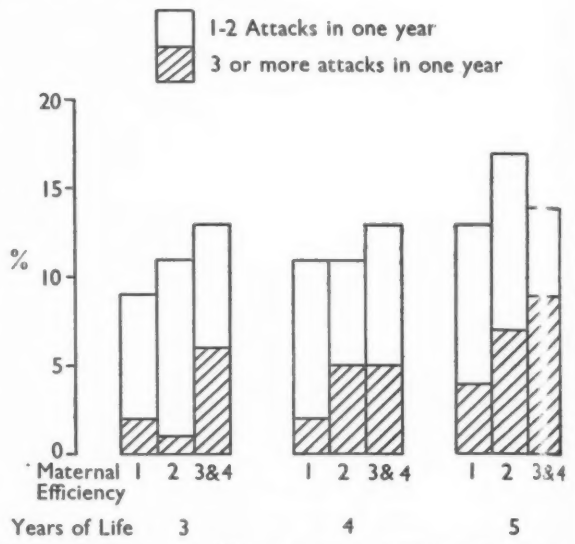


FIG. 2.—Proportion of children, by maternal grade, suffering from at least one attack of tonsillitis.

Infections of Ear, Nose and Throat

In the first two years of life, infections of ear, nose and throat accounted for 14% of all medical illnesses compared with 20, 27 and 34% in the next three years.

Tonsillitis. Of the total group, 27% had one or more attacks of acute tonsillitis during the three-year period. Mild sore throats with little constitutional disturbance were not included. Fig. 2 shows the percentage of children, by maternal efficiency, who suffered from at least one attack of tonsillitis in each year from 2 to 5, and the percentage of children having three or more attacks in any one year. With declining maternal standards, the incidence of infection rises, and also the number of cases of recurrent tonsillitis.

Of the 514 children followed through to 5 years, 53 (10·3%) had tonsils and adenoids removed before the fifth birthday, and in four more adenoidectomy only was performed. Children from the

TABLE 1
REMOVAL OF TONSILS AND/OR ADENOIDS: INCIDENCE BY MATERNAL EFFICIENCY GRADE

Maternal Efficiency	% Children Having had Adenoidectomy With or Without Tonsillectomy		
	3 Years	4 Years	5 Years
1	1·0	5·6	10·1
2	0·9	5·2	11·4
3 and 4	1·8	3·5	13·3
Number of cases ..	6	26	57

poorest homes were most likely to have had this operation performed (Table 1).

Table 2 gives the main indication for which the operation was carried out, with an assessment of the degree of improvement, if any, noticed after operation. This was necessarily rough as it was based mainly on the mother's own report. In 10 cases insufficient time has elapsed since the operation to make any assessment. In three cases there was no obvious reason why the operation was performed. In all, 53% showed definite improvement after operation, 17% some improvement and 30% no obvious improvement.

TABLE 2
INDICATIONS FOR ADENOIDECTOMY AND/OR TONSILLECTOMY

Main Indication for Operation	No. of Cases	Improvement			
		Definite	Some	None	I.T.*
Recurrent tonsillitis ..	31	19	5	2	5
Adenoidal, frequent head colds	13	4	2	4	3
Otitis media	8	2	1	3	2
Deafness	2	—	—	2	—
?	3				
Total	57	25	8	11	10

* Insufficient lapse of time since operation to make any assessment.

Otitis Media. During the first five years of life, 63 children had one or more episodes of purulent otorrhoea with or without earache. In a further 15 a diagnosis of otitis media had been made by the family doctor in the absence of discharge. Thus, a total of 78 children (15%) were reported as having had a middle-ear infection. Other cases of non-recurrent earache which, from the history, might have been due to tonsillitis or carious teeth, were not included, nor were a few others where the diagnosis had been made without aural examination. Most of the cases of otitis media without discharge which had been definitely diagnosed were reported from the better type of home, and it seems likely that there was under-reporting from the poorer homes. Here it was not unusual to find that earache had been

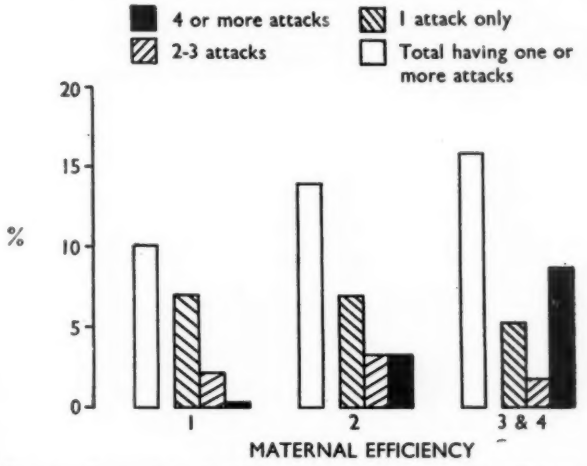


FIG. 3.—Proportion of children analysed by maternal efficiency suffering from one or more attacks of purulent otorrhoea during the first five years of life.

treated with aspirin and warm oil drops, often prescribed by the local chemist, the doctor only being called in cases of persistent discharge or marked constitutional disturbance. The recorded incidence of 15% of total children affected is probably an underestimate. In the Newcastle survey (Miller, Court, Walton and Knox, 1960), 19% of children were affected before the age of 5 years.

Fig. 3 shows the percentage of children by maternal efficiency grade having one or more attacks of purulent otorrhoea in the first five years of life, and the percentage having (1) one single attack (2) two or three separate attacks or exacerbations of one attack and (3) four or more distinct attacks or exacerbations.

The incidence of affected children rises with declining maternal standards, but a more marked difference is found in the proportion of affected children having four or more attacks. In the best homes over 70% of affected children had one attack only. In the worst homes 50% had four or more attacks or exacerbations.

Table 3 shows the number of cases in which there

TABLE 3
CO-EXISTING INFECTIONS AT TIME OF FIRST ATTACK OF PURULENT OTORRHOEA

Infections	No.	%
Measles	8	13
Tonsillitis	7	11
Upper respiratory infection	3	5
Lower respiratory infection	3	5
Fractured skull	1	1
None, but child subject to repeated infections	12	19
None, child healthy	29	46
Total	63	100

TABLE 4

AGE OF FIRST ATTACK OF PURULENT OTORRHOEA BY MATERNAL EFFICIENCY GRADE

Maternal Efficiency	Age (Years)			Total	No. of Cases
	<1 (%)	1–2 (%)	3–5 (%)		
1	13·8	24·1	62·1	100·0	29
2	25·0	31·2	43·8	100·0	16
3 and 4	33·3	22·2	44·5	100·0	18

was coexisting infection at the time of the first attack of purulent otorrhoea. In 41 of 63 cases (65%) there was no other infection reported, although 12 of these children, all from poor homes, were subject to repeated infective illness of one sort or another before and after the initial attack of otitis media. Table 4 gives the age of the first attack of purulent otorrhoea by maternal efficiency. One-third of affected children from the poorest homes had their first attack before the first birthday.

Later, it is hoped to obtain results of audiometric testing in school for all children in the survey attending Edinburgh Corporation schools. So far, 10 of the 63 children have been tested and of these eight have some impairment of hearing.

Specific Fevers

Table 5 gives the number of cases of specific fevers for each year of life up to 5 years, occurring in the 514 children who have been followed up to this age; 265 were first-born children and 249 had older siblings. As children with older siblings are likely to contract these infections at a younger age, the cases are divided into those occurring in first- and later-born children and totals are given for all children.

Measles. Measles was by far the most common of the immunizing diseases recorded. More than one-half of all children in the survey had contracted

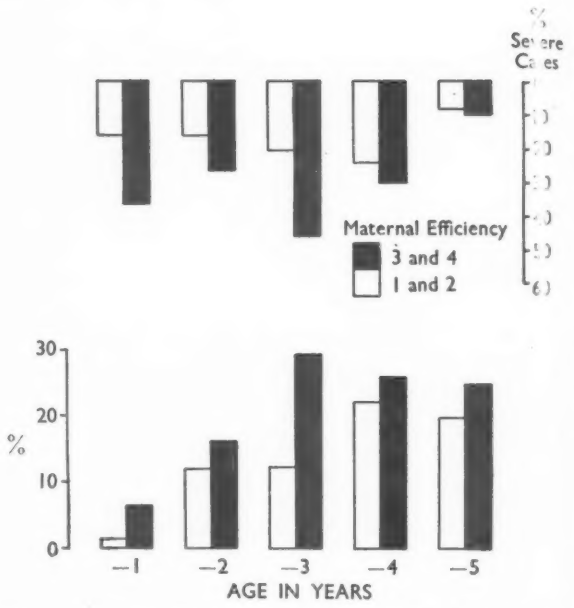


FIG. 4.—Incidence of measles per 100 susceptible children by year of life and maternal efficiency, and proportion of cases considered severe.

measles by their fifth birthday. The incidence of measles, the severity of the disease and the age at which it was contracted, all varied with social class and place in the family.

For all types of home the incidence was lower for first-born children as compared with later-born below the age of 3 years. In the poorest homes the incidence in first-born children after the age of 3 was as high or higher than in later-born children. The proportion of first-born children varied with maternal efficiency grade, being 60% in those cases graded 1, 46% in cases graded 2 and 35% where efficiency was graded 3 or 4.

Fig. 4 shows the case incidence of measles for each year of life per 100 susceptible children (i.e.

TABLE 5

NUMBER OF CASES OF SPECIFIC FEVERS IN 514 CHILDREN BY YEAR OF LIFE AND PLACE IN FAMILY

	Years of Life										Total			% Total Children Contracting Infection up to 5 Years		
	1st		2nd		3rd		4th		5th							
	First-born	Later-born	First-born	Later-born	First-born	Later-born	First-born	Later-born	First-born	Later-born	First-born	Later-born	All Cases	First-born	Later-born	All Cases
Measles	6	8	23	44	35	31	38	45	31	26	133	154	287	50·2	61·8	55·8
Chicken-pox	1	12	2	12	8	14	12	12	11	21	34	71	105	12·8	42·2	20·4
Whooping cough ..	5	8	8	14	6	15	3	15	2	7	24	59	83	9·1	23·7	16·1
Mumps	—	2	4	4	4	5	11	13	17	11	36	35	71	13·6	14·1	13·8
Rubella	1	1	4	1	10	17	8	17	4	5	27	41	68	10·2	16·5	13·2
Scarlet fever	—	—	—	—	3	—	3	2	5	—	11	2	13	4·2	0·8	2·5
Total	13	31	41	75	66	82	75	104	70	70	265	362	627			

TABLE 6

INCIDENCE OF WHOOPING COUGH IN PROTECTED AND UNPROTECTED CHILDREN BY MATERNAL EFFICIENCY GRADE

Maternal Efficiency	Immunized Children			Non-immunized Children		
	+	?	−	+	?	−
1 and 2:						
Incidence per 100 children	11·3	5·2	83·4	24·0	—	76·0
Per cent. total cases considered severe	9·3			11·1		
3 and 4:						
Incidence per 100 children	9·8	—	90·2	33·3	13·9	65·3
Per cent. total cases considered severe	50·0			41·7		

those who had not already contracted the disease) by maternal efficiency grade. The incidence has been standardized for place in family (i.e. the incidence has been calculated which would be expected if the proportion of first- and later-born children were identical for all maternal efficiency groups). In each year of life, more especially in the first three, susceptible children from the poorest homes are more likely to contract measles. The incidence is maximal for these children between 2 and 3 years, compared with a maximum between 3 and 4 years for children from better homes. Fig. 4 also shows the proportion of cases considered severe (i.e. those having considerable constitutional disturbance and prolonged convalescence with or without a complicating otitis media, bronchitis or pneumonia).

In each year of life the proportion of severe cases is much higher for children from the poorest homes. In all types of home the highest proportion of severe cases occurred not in infancy, but at the age of maximum susceptibility. The number of severe cases dropped considerably after the age of 4 years.

Whooping Cough. A comparison of the effect of environmental factors on the incidence of whooping cough is complicated by the fact that in maternal efficiency grade 1, 88% of children received protective immunization against whooping cough before their second birthdays, 64% in grade 2 and only 38% in grades 3 and 4.

Of the total sample, 14% had contracted whooping cough by their fifth birthday. Eighteen other children had had an episode of spasmodic cough, worse at night, lasting for four to eight weeks, but without whoop, vomiting or constitutional disturbance. In no case was there any obvious cause for the cough, such as post-nasal drip. Seventeen cases occurred in immunized children from good homes and one in an unimmunized child from a poorer home. If these cases are included as whooping cough, the percentage of total children affected rises to 20%. In the Newcastle survey 44% of children had contracted whooping cough by the age of 5 years. Only 56 of a total of 847 Newcastle children (7%) had been given protective immunization. Of these, 11 contracted the disease (20%). In the Edinburgh sample incidence was highest in later-born children from the poorest homes and maximum in the second year. In better homes (i.e. maternal efficiency grades 1 and 2), the maximum incidence was between 3 and 4 years and then only reached one-half that for children from grade 3 and 4 homes one year earlier.

Table 6 gives the case incidence up to 5 years by maternal efficiency for children who had and had not received protective immunization and also the percentage of affected children in whom the disease was considered severe.

Amongst unprotected children the incidence was higher in those from poor homes; this was not seen in protected children.

When an attack had occurred the chance of its being severe did not appear to differ significantly for protected or unprotected children, though in both groups the incidence of severe and complicated cases was very much higher for children from poorer homes.

In the two-year analysis no statistically significant difference could be found in rate of attack or incidence of severity between protected and unprotected children when maternal efficiency was taken into account. This is due to the fact that the majority of children from good homes where protection is common tend to contract the disease after this age, and the majority from poor homes where immunization is uncommon contract the disease before 2 years. The difference in incidence rates between protected and unprotected children could not be separated from the effect of maternal efficiency. When all cases occurring up to 5 years are considered a significantly lower incidence is seen in protected children ($\chi^2 = 11{\cdot}993$; $p = <0{\cdot}001$), although the proportion of severe attacks is not affected even if the queried cases are included as true cases of whooping cough.

TABLE 7
OTHER EYE DEFECT ASSOCIATED WITH SQUINT

Birth Weight	Hypermetropia With or Without Astigmatism	Myopia With or Without Astigmatism	Myopia With or Without Other Abnormality	Other Defect	No Refractive Error	No Knowledge
4·8 and under	5	5	3	1	2	3
4·9 and over	10	1	—	2	5	1

Other Specific Fevers. No obvious social gradient was found in the incidence of chicken-pox, mumps or rubella.

In chicken-pox maximum incidence was recorded in the fifth year. At every age, incidence was much higher for later-born children. The incidence of rubella was also rather higher for later-born children with most cases occurring between 2 and 4 years. Mumps was recorded most frequently in the fifth year. Here no difference was found between incidence in first- and later-born children.

Convulsions

Twenty-five surviving children have a history of one or more episodes of convulsions in the period between discharge from maternity hospital and 5 years.

This incidence of 4·9% is lower than that recorded in the Newcastle survey (Miller *et al.*, 1960), where 5·8% of children surviving to 5 years gave a history of convulsions. The recording of morbidity data was more accurate in the Newcastle survey and it is probable that the Edinburgh figure is an underestimate. Seven of the 25 children are mentally handicapped; of these, three have recurrent convulsions. Eighteen come within the normal range of intelligence and attend normal school; three of these have recurrent convulsions.

The birth weight distribution of the 15 children who have a history of not more than two convulsive episodes does not differ from that of the total sample, three being less than 4½ lb. at birth, seven between 4½ and 5½ lb. and five over 5½ lb. All the mentally retarded children with fits were premature, six of them being less than 4½ lb. at birth.

The birth history of the 15 mentally normal children with non-recurrent convulsions has been examined. In six cases there was a history of complicated delivery. Three of these were delivered by mid-cavity forceps, one on account of foetal distress and two owing to delay in the second stage. In one case manual rotation was performed. Three others were delivered by breech extraction, two on account of second stage delay and one due to deep transverse arrest. The incidence of 40% assisted delivery compares with 20% in the total sample. In spite of the small numbers the difference is on the border of statistical significance ($\chi^2 = 3{\cdot}047$). Three of the six children with complicated delivery showed abnormal post-natal signs as did two others who were delivered spontaneously by vertex and breech respectively. The incidence of abnormal post-natal signs in the total sample was 14·2% compared with 33·3% in the group who later had febrile convulsions. This difference can be considered statistically significant ($\chi^2 = 4{\cdot}203$). Although on so few cases there is reluctance to draw any definite conclusions, the findings suggest that a predisposition to later febrile convulsions may result from minor brain damage at birth.

Squint

Thirty-eight cases of persisting squint (7·4%) were noted during the first five years of life. In seven further cases a definite squint was noticed over a period of three to six months or longer, but cleared spontaneously without treatment, and no error of vision has been reported so far in these children after school medical examination. Transient squints which are common in early infancy and may be prolonged in small premature infants have not been included.

Persisting squint was more commonly found in small prematurely-born children, being 16·3% of those 3½ lb. or less at birth, 11·0% of those between 3½ and 4½ lb. and 5·2% of those over this birth weight. The incidence was no higher for twins than singletons once allowance had been made for birth weight.

The incidence in larger premature and full-term children corresponds closely to that found in the Newcastle survey.

Associated errors of refraction and other eye defects are shown in Table 7 for those above and below 4½ lb. at birth.

Myopia was the commonest refractive error found in the small prematures and hypermetropia in those over 4½ lb. at birth.

Twelve of the 38 children with squints were mentally defective (I.Q. <70), or border-line defectives (I.Q. 70-79). All the eight children with myopia were mentally retarded, and two of those

with hypermetropia. Two of these retarded children had recurrent epileptic fits and one was a case of congenital cerebral palsy.

Six children had other congenital defects apart from mental retardation. In these cases it appears that the eye defect is part of a general picture of abnormal development.

Accidents

During the age period 2 to 5 years, 39 cases of accident or injury were treated in hospital. These are set out by cause and maternal efficiency grade in Table 8. The highest accident rate in the first five years was recorded for the second year of life (4·4%); in the third, fourth and fifth years it was 3·3, 2·3 and 1·9%.

In the analysis of data up to 2 years, no difference was found in accident rates in different types of home. Up to that age the majority of accidents occurred within the house. After the age of 2 years there is a significant difference between accident rates in homes where maternal efficiency was considered very good, and homes where efficiency rated as good, fair and poor ($\chi^2 = 8{\cdot}666$; $p = <0{\cdot}01$). There is also a difference in the type and severity of accidents. Of 13 accidents occurring in grade 1 homes, 11 required stitches for cuts and two were more serious. Of the 26 accidents occurring in other homes, eight were relatively trivial and 18 more serious.

Eleven of the 13 accidents in grade 1 homes occurred in the house or garden. Fifteen of the 26 other accidents occurred in the street. In six of these cases the child was knocked down by a car. The difference by type of home appears to be due to the fact that pre-school children from the middle class and superior working-class homes where nearly all mothers were graded efficiency 1, are allowed considerably less freedom outside the home than children from average or poor working-class homes. Permission to play in the street was not due to poor housing. In all but one case children injured in the streets lived in good houses nearly all of which had gardens. The child living in a suburban local authority housing scheme is more likely to be allowed out to play in the pre-school period than the child living in overcrowded or condemned property in the town. This was noticed in particular in the average working-class home where maternal efficiency was considered good. This type of mother did not allow her pre-school children out to play alone if she lived in slum property, but did not insist on the children remaining in the garden if she moved to a local authority estate.

TABLE 8

ACCIDENTS REQUIRING HOSPITAL TREATMENT IN 514 CHILDREN AGED 2 TO 5 YEARS, BY MATERNAL EFFICIENCY GRADE

Accident	Efficiency Grade			Total
	1	2	3 and 4	
Cuts requiring stitches ..	11	2	5	18
Head injuries	—	5	—	5
Burns and scalds	1	—	4	5
Fractures	—	3	2	5
Crush injuries and penetrating wounds	1	2	—	3
Swallowed foreign body ..	—	—	1	1
Poisoning	—	1	—	1
Drowning	—	1	—	1
Total	13	14	12	39
Percent. children at risk ..	4·5	12·3	10·6	7·6

Enuresis

The age at which children become reliably dry by day and night was found to depend on sex, birth weight and type of home. Full toilet history was obtained for 518 children.

A child is considered to be reliable by day when he is able to take responsibility for his own toilet requirements either by telling his mother or by going to the toilet himself. He can be allowed out to play without fear of accidents. A child is considered reliable at night when he is dry except for an occasional accident without being lifted. He may either go through the night without needing to micturate or else wake himself if he needs the toilet.

Table 9 gives the ages by which girls and boys were reported to be reliably dry by day and night for those over 4½ lb. at birth and those who were below this weight. Small prematurely-born children acquire sphincter control later than those over 4½ lb. at birth. This is due, in part, to an excess of mentally retarded children, but not entirely, as a difference was still seen by birth weight when children with an I.Q. of less than 100 were omitted. Part of the difference can be attributed to an excess of poor homes in the small premature group, but within each social group the small prematures were later to acquire control. No difference was found by birth weight over 4½ lb. Girls became reliable by day earlier than boys; 52% of girls were dry by 2 years compared with 40% of boys. In the 2-year analysis (Drillien, 1959), a higher percentage of both girls and boys were reported as being dry at 2 years. However, on further questioning at 3 years, it was found that a number who had been reported as reliable at 2 had later relapsed. In the 2-year analysis only singletons were considered. Twins, on average, acquire sphincter control later than singletons of like birth weight. This appears

TABLE 9

AGE BY WHICH 514 CHILDREN WERE REPORTED AS RELIABLY DRY, BY BIRTH WEIGHT AND SEX

Sex	Birth Weight lb. oz.	% Reliable by Day (Years)				Not Reliable At 5 Yrs (%)	% Reliable by Night (Years)				Not Reliable At 5 Yrs (%)
		2	3	4	5		2	3	4	5	
Female	4 8 and under	35	89	99	100	—	20	71	86	96	4
	4 9 and over	59	90	98	99	1	30	75	87	92	8
	Total	52	90	98	99	1	27	74	87	93	7
Male	4 8 and under	27	74	92	96	4	8	38	70	78	22
	4 9 and over	46	95	98	99	1	21	61	81	88	12
	Total	40	89	97	98	2	17	54	78	85	15

to be due to the fact that toilet training tends to start later for twins. By 3 years, there was no difference in the proportion of girls and boys reliable by day. A more marked sex differential was seen in the age at which children became reliable by night. At 5 years, 7% of the girls (19 cases) were still wet at night and 15% of the boys (37 cases). The overall incidence of 11% corresponds quite closely with the minimal estimate of 9% enuretic at 5 years in the Newcastle survey.

Table 10 gives the ages at which all children were reported as reliable by day and night by maternal efficiency grade. Children under 4½ lb. at birth have been excluded as these acquire control later, and this group contains an excess of children in grade 3 or 4 homes. At 5 years 7% of children from the best homes were still unreliable at night compared with 16% in the worst homes.

At 2 years only 30% of children from the worst homes were reliable by day compared with 60% in the best, but this is not surprising as the age of starting toilet training was much later in the former; over one-quarter of these children had never been attempted on the pot at 2 years.

Of the 37 boys who were still bed wetting at 5 years, 19 were wet on average at least six nights out of seven and had never gone longer than two or three days without being wet. Fourteen were wet less often, some could be kept dry by lifting, and some had had dry periods of several weeks. Four others who had been dry for three to six months later reverted to bed wetting. Among the 19 girls, eight were wet nearly every night, eight less often and three had reverted. In the seven children who became enuretic after apparent establishment of control, this appeared to be connected with an emotional disturbance; the arrival of a new baby in two cases, severe marital discord in three and school entrance in two.

Of the 22 children who had never been dry, five were mentally defective and six more came from very poor homes, where wet beds were considered an unavoidable evil; 15 of these children did not acquire day control before the age of 4 years.

Only three of the 22 children who were wet less often came from very poor homes and none were mentally defective. In the majority control during the day had been established before the age of 3 years.

Infective Illness in Day Nurseries and Nursery Schools

In the first two years of life, 17 children attended day or residential nurseries for periods of six months or longer. After the age of 2 the number of children attending day nursery, play centre or nursery school increased each year. Between 4 and 5 years 83 children were in regular attendance at one of these centres. The amount of infective illness suffered

TABLE 10

AGE BY WHICH CHILDREN OVER 4½ LB. AT BIRTH WERE REPORTED AS RELIABLY DRY, BY MATERNAL EFFICIENCY GRADE

Maternal Efficiency	% Reliable by Day (Years)				Not Reliable At 5 Yrs (%)	% Reliable by Night (Years)				Not Reliable At 5 Yrs (%)
	2	3	4	5		2	3	4	5	
1	60	96	100	—	—	29	76	89	93	7
2	52	95	99	—	1	28	62	80	88	12
3 and 4	30	78	94	97	3	14	53	75	84	16

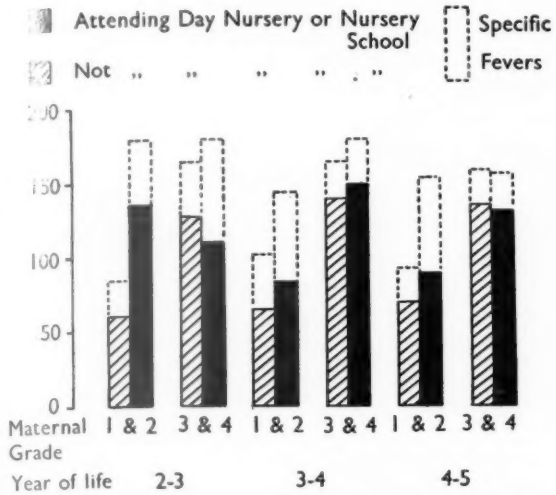


FIG. 5.—Number of incidents of infective illness per 100 children attending day nurseries, compared with those at home, by maternal efficiency and year of life.

by nursery children has been compared with that suffered by children from similar backgrounds who spent the same period within their own homes. Up to the age of 3, all nursery children in the survey were attending local authority nurseries. The child was given a vacancy either because his mother needed to work as a result of death, desertion, unemployment or illness of the father, or because the home environment was so poor as to be considered seriously detrimental to the child's health and development. A few were admitted to residential or day nursery on account of chronic illness or death of the mother. Others who were admitted for short periods because of temporary domestic emergency have not been included. After the age of 3 an increasing number of children attended play centre, local authority nursery school or private kindergarten in the absence of any special need.

Fig. 5 shows the relative number of infective incidents for home and nursery children by maternal efficiency grade at ages 2 to 5 years. Specific fevers are shown separately from other infective illness.

At each age nursery children from the best homes showed a higher infection rate. This was most marked between 2 and 3 years when twice as many incidents were recorded for nursery children as for children at home. This may be due partly to the fact that admission to a nursery at this age is dependent on need, and even though maternal efficiency is rated as good or very good, the fact of nursery admission indicates a degree of financial hardship in these homes as compared with mothers of like efficiency who did not need to work. After the age of 3 the increased infection rate in nursery children resulted mainly from an excess of specific fevers.

Nursery children from poorer homes had no more infections than home children at any age apart from a small increase in incidence of specific fevers. It appears that any added risk of exposure to infection is offset by improvement in general health resulting from nursery diet and routine.

Hospital Admission for Medical Reasons

Forty-eight hospital admissions were recorded for the age period 2 to 5 years, 30 of them being in the third year.

The number of hospital admissions fell steadily from 12·5 admissions per 100 children in the first year of life to 1·6 in the fifth.

Table 11 shows the total hospital admissions for medical illness and the division by diagnostic category and by year of life up to the age of 5 years.

Over one-half of total admissions were on account of lower respiratory and gastro-intestinal infection, and nearly 90% of medical illnesses necessitating hospital admission were due to infection.

One mentally defective child (a twin boy, birth weight 3 lb. 7 oz.) died in an institution at the age of 4 years; the cause of death was meningococcal septicaemia.

TABLE 11

HOSPITAL ADMISSIONS BY CAUSE IN THE FIRST 5 YEARS OF LIFE

Hospital Admissions	Age (Years)				
	1	2	3	4	5
Respiratory infection	28	17	5	1	2
Gastro-intestinal infections ..	23	5	6	—	1
Infection of ear, nose and throat	3	6	3	2	1
Specific fevers	3	10	9	5	2
Other infections	7	4	5	1	1
All other causes	7	8	2	1	1
Total	71	50	30	10	8
Per cent. children at risk ..	12·5	8·9	5·8	1·9	1·6

Effect of Rehousing on Health

The effect of rehousing on health has been studied in 64 children who were observed for at least one year before rehousing and one year after. The majority were rehoused in new local authority houses, and a few moved to privately owned property. The houses vacated consisted of one or two room dwellings with few conveniences apart from a sink, cold water and a gas cooker. Toilets were commonly shared with other tenants. Many houses were damp and in poor repair.

As at 2 years, any assessment of the effect on

health of poor housing was difficult because poor housing and a low standard of maternal care commonly went together. In addition, of the 64 children considered here 48 were rehoused between the age of 18 months and 2 years and it has been noted that the incidence of recurrent infection, so common in poor homes, falls markedly after this age in all types of housing.

Fifty-five other children were still living in very poor accommodation at 4 years. Twenty-three families (with one exception all graded 3 and 4 for maternal efficiency) have not applied for rehousing, either because they appear satisfied with present accommodation or because they are unable to afford higher rents.

The incidence of infective illness between 2 and 5 years (excluding specific fevers) was found to be almost identical in those children who had been rehoused and those awaiting rehousing, where maternal care was considered good or very good. Where maternal care was fair or poor, the incidence of infection was one and a half times as high in those who had been rehoused. However, this excess of infection in the rehoused children is not enough to be statistically significant. It may be due in part to the larger family size of those poor families who have been rehoused, but even so the figures do not suggest that rehousing by itself leads to improvement in health as measured by incidence of infection. Rehousing involves the family in increased expenditure on rent and maintenance and often in the first two or three years in quite heavy hire-purchase repayments for new furnishings and floor covers. Where the father earns a low wage, is working short time or is unemployed, there is less money available for food, clothing and coal, which may well offset the initial advantages of a new house.

In general, the mothers took into the new homes the standards of care and household management observed in the old, but in nine of the 64 cases maternal standards quite obviously rose after rehousing. These mothers and several others remarked on an improvement in their own health and well-being after rehousing.

Summary

The health history has been studied of over 500 premature and maturely born children in Edinburgh, between the ages of 2 and 5 years.

Respiratory illness. The incidence of lower respiratory infection showed a marked decline in the third year. The striking association between lower respiratory infection and inadequate maternal care noted in the first two years of life was not so obvious after this age.

Only four out of 35 children with a history of repeated lower respiratory infections in the first two years, showed an excess in expected infection rate after this age.

Infections of ear, nose and throat. The incidence of such infections increased steadily after the age of 2 years, and between 4 and 5 years accounted for one-third of all medical illness.

Of the total group 27% had one or more attacks of acute tonsillitis between 2 and 5 years. The incidence increased with declining maternal standards as did the number of affected children having recurrent attacks.

Over 10% of the group had tonsils and/or adenoids removed before the fifth birthday. In one half of cases the operation appeared to be beneficial. In 30% no obvious benefit resulted. A middle-ear infection was recorded in 15% of the group before the fifth birthday. Incidence was higher where maternal care was judged unsatisfactory. Recurrent purulent otorrhoea was much more common in poor homes.

Specific fevers. One half of the group had contracted measles by 5 years of age. Incidence was higher in later-born children from unsatisfactory homes and the proportion of severe cases was much higher in such homes.

A statistically significant excess of cases of whooping cough was found in children who had not received protective immunization. Once contracted, previous immunization did not appear to alter the chance of the attack being a severe one.

No social gradient was found in the incidence of other specific fevers.

Convulsions. Of surviving children, 5% had one or more convulsive episodes before the fifth birthday. A consideration of the birth history of those with normal intelligence and non-recurrent febrile convulsions suggests that minor brain damage at birth may result in a predisposition to febrile convulsions.

Squint. Persisting squint was three times as common in children 3½ lb. or less at birth and twice as common in those between 3½ and 4½ lb. as in those over this birth weight. Myopia was the commonest refractive error found in the small prematures and hypermetropia in those over 4½ lb. at birth.

Eight of the nine cases of myopia were mentally retarded. Six other children of a total of 38 had

other congenital abnormalities apart from mental defect.

It is suggested that in the prematurely born the eye defect is commonly a part of a general picture of abnormal development.

Accidents. After the age of 2 years a significantly lower accident rate was found in middle-class and superior working-class homes. The excess in other types of home resulted from accidents occurring in the streets.

Enuresis. Sex, birth weight and type of home all affected the age at which children acquired sphincter control by day and by night. At 5 years, 7% of girls and 15% of boys were not reliably dry at night.

Infective illness in day nurseries and nursery schools. Children from good homes contract considerably more infective illness between 2 and 3 years of age when attending a nursery; after this age the excess in infective illness is much less. Children from poor homes have no more infective illness at any age when attending nurseries than do those remaining in their own homes.

Hospital admissions. Hospital admissions for medical illness fell steadily from 12·5% in the first year of life to 1·6% in the fifth. One half of total admissions were on account of lower respiratory and gastro-intestinal infections.

The effect of rehousing on infective illness. No difference in the incidence of infective illness could be found between children who had been rehoused or were awaiting rehousing. It is suggested that the added financial burden of a new house may offset the advantages of good accommodation.

It is a pleasure to thank Professor R. W. B. Ellis for his assistance and encouragement throughout.

This investigation was carried out during the tenure of a Senior Research Fellowship of the Mental Health Research Trust Fund with an Expenses Grant from the Scottish Hospital Endowments Research Trust.

References

Drillien, C. M. (1958). A longitudinal study of the growth and development of prematurely and maturely born children. Pt. 1: Introduction. *Arch. Dis. Childh.*, **33**, 417.

—— (1959a). Pt. IV: Morbidity. *Ibid.*, **34**, 210.

—— (1959b). Pt. V: Patterns of maternal care (A study of child rearing in Scotland). *Ibid.*, **34**, 487.

Miller, F. J. W., Court, S. D. M., Walton, W. S. and Knox, E. G. (1960). *Growing up in Newcastle upon Tyne.* Published for the Nuffield Foundation by Oxford University Press, London.

CEPHALIC SPREAD OF NEUROBLASTOMAS IN CHILDREN

BY

W. I. B. ONUIGBO

From the Pathology Department, The University and Western Infirmary, Glasgow

(RECEIVED FOR PUBLICATION JANUARY 11, 1961)

The two classics on the tumours now known as neuroblastomas date back only to the beginning of this century. First, Pepper (1901) published 'A study of congenital sarcoma of the liver and adrenal'. One of his six cases was a girl of 9 months whose adrenal tumour had spread not only to the liver but also to the skull. Not long afterwards Hutchison (1907) discussed the cephalic spread of neuroblastomas in children.

In 1910 the University of Edinburgh accepted Frew's thesis that neuroblastomas usually metastasize ipsilaterally to the orbit and skull (Frew, 1911). Today, however, his conclusions still divide the profession. Thus, Duke-Elder (1952), among others, is of the view that the orbital metastasis 'appears first with remarkable regularity on the side corresponding to the affected adrenal', whereas Pack, Horning and Ariel (1952) maintain, as do others, that the site of the primary neuroblastoma 'could in no way be found attributable for the site or number of metastases', although Willis (1952) concedes that 'there is only a small modicum of truth in this hypothesis'.

The purpose of this paper, therefore, is to re-examine the available evidence and to evaluate the lateralization of cephalic metastases occurring in neuroblastomas.

Investigation

This paper analyses 132 neuroblastomas metastasizing to the orbit and skull in children. One hundred and one cases were collected from the literature, care being taken to exclude duplicated cases; 22 were obtained from the records of The Hospital for Sick Children, Great Ormond Street, London, and nine from the Royal Hospital for Sick Children, Yorkhill, Glasgow.

The origin of the primary tumour on the right or left side of the body was first ascertained. Next, it was noted whether the ipsilateral or contralateral orbit was involved, the criteria of involvement being combinations of exophthalmos, ecchymosis, strabismus, papilloedema, and para-orbital swellings. When the orbital deposits were bilateral, the side first involved was determined. If this was not expressly stated, then the side showing the grosser involvement was taken as that which was invaded earlier. Lastly, if orbital metastases were absent or inadequately described, then recourse was had to the skull in order to find out which side contained a secondary deposit or exhibited a greater amount of such deposits.

Results

The Table summarizes the topographical distribution of metastases in 132 adequately described cases of neuroblastoma. The trend towards ipsilateral invasion was manifest in 86 cases, while in 46 the trend was contralateral.

Instead of the chance of metastasis being equal between the ipsilateral and the contralateral orbit and skull, there seems to be a double chance of deposits being found ipsilaterally. The χ^2 test of goodness of fit (between *observed* ipsilateral frequency and *expected* ipsilateral frequency of one half) may be applied. Following Fisher and Yates (1957), six classes are distinguished in the Table, the classes being grouped so as to ensure that the expected frequency is not less than 5; the summation is taken over all classes. Accordingly, $\chi^2 = 114{\cdot}223 - 86 = 26{\cdot}223$. Since there are 5 degrees of freedom in the above six classes, this χ^2 value is highly significant for the probability of this result being due to chance is 0·001. We may conclude, therefore, that in all probability neuroblastomas spread preferentially to the orbit and skull on the same side.

Discussion

For the above conclusion to be valid, the series must be unbiased. First, there must be a faithful inclusion of all the adequately described cases which I came across. That the series is in all probability free from biased selection is attested to by the fact that as many as 101 cases have been collected from

TABLE

TOPOGRAPHICAL DISTRIBUTION OF CEPHALIC METASTASES IN 132 NEUROBLASTOMAS, WITH CALCULATION OF χ^2

Source	Ipsilateral Metastases	Contralateral Metastases	(Observed Ipsilateral)^2 / Expected Ipsilateral
Targett (1888), Cohn (1894), Aisenstein (1905), MacCarty (1905), Ogden and Mathews (1906), Bruck (1905), Tileston and Wolbach (1908), Mann (1909), Platt (1911), Wessely (1919), Gunby (1920), Fleming and Davidson (1924), Lederer (1926), Sturtevant and Kelly (1927), Gibson (1927), Henle (1928), Greig (1929), Alyea (1933), Redman, Agerty, Barthmaier and Fisher (1938), Kuhn (1939), Donnally, Rice and Giddens (1939), Greenthal and Epstein (1939), Clark (1939), Karsner (1942), Rosendal (1942), Bothman and Blankstein (1942), Pi (1944), Ford (1945), Ackerman and Regato (1947), Cox (1948), Loomis and Loomis (1949), Boyd (1950), Poore, Dockerty, Kennedy and Walters (1951), Hyman and Sztramski (1955), Grogono (1956), Reiquam, Beatty and Allen (1956), Gupta and Roy (1957), Leach (1957), and Busfield (1958) .. .. *one each*	39		54·325
Chaffey (1885), Bendixen and Lamb (1926), Holmes and Dresser (1928), Klein (1932), Law (1932), Cust (1937), Kato and Wachter (1938), Lucas (1940), Guibor (1942), Riad Bey (1942), Barden (1943), Schroder (1949), Harrison, Warres and Fust (1950), Pack *et al.* (1952), Trotter and Winchell (1954), Seaman and Eagleton (1957), and Maclean (1959) .. .. *one each*		17	
Boyd (1926)	1	1	
Tidswell and Sear (1933)	1	1	
Thompson (1942)	1	1	5·000
Hansen (1953)	1	1	
Sladden (1953)	1	1	
Carter (1921)	2	0	
Wollstein (1928)	2	0	
Lewis and Geschickter (1934)	2	0	11·635
Chont (1941)	2	0	
Hartung and Rubert (1935)	0	2	
Oberkircher, Staubitz and Parmenter (1953)	2	1	
Shaffer (1947)	2	2	6·000
Blacklock (1934)	2	3	
Frew (1911)	5	2	18·616
Hutchison (1907)	6	0	
The Hospital for Sick Children, London	13	9	18·647
Royal Hospital for Sick Children, Glasgow	4	5	
Totals	86	46	114·223

the literature; the estimated total of published cases is 450 (Pack *et al.*, 1952) and about 20% spread cephalically (Stowens, 1959).

Another source of error was borne in mind. Poore (1949) made the sound suggestion that in interpreting figures collected from the literature the possibility must be considered that 'cases may be more likely to appear in the literature if they describe the "typical" syndromes, including the asymmetry advanced by Frew and widely quoted by others'. However, I am persuaded that at no time did Frew's hypothesis of asymmetry—preferential ipsilateral metastasis—enjoy such common acceptance that it influenced the type of case getting into print. Indeed, it seems to me that preconceptions do not appear to have inclined authors to record cases which harmonize with the view that they happen to hold. Thus, the case reported by Karsner (1942), who was opposed to Frew, exhibited initial ipsilateral invasion of the orbit; and, conversely, that reported by Cust (1937), who supported Frew, showed invasion of the contralateral orbit.

Perhaps, the issue of metastasis of neuroblastomas is still fogged because, as Steward (1958) pointed out, few doctors see enough cases to have a clear picture of the natural history of the disease. Hitherto, reports refuting or supporting Frew's concept of ipsilateral cephalic metastasis have been based upon only a few cases. In the present contribution, however, the accumulation of a large enough series has made statistical evaluation possible.

Frew was basically right, but he erred by overstating his case. Since he asserted that cephalic metastasis was ipsilateral 'in nearly every instance', every case which, thereafter, did not spread ipsilaterally was held to negative his hypothesis. To me, the position that should now be taken is that *neuroblastomas metastasize preferentially to the ipsilateral orbit and skull to a statistically significant extent*.

Clearly, arterial dissemination *per se* can hardly account for this pattern. Some authorities, notably Neale (1954) and Belt (1959), still agree with Frew that this pattern is suggestive of lymphogenous dissemination, but most others now indict the blood stream. In particular, ever since Batson (1940) brought the vertebral venous system into the limelight, opinion has veered in favour of metastasis by this route to the head. Thus, before Batson's epochal work, Boyd (1926, 1932) was satisfied that

neuroblastomas spread by way of the lymphatics to the orbit, but, subsequently, Boyd (1958) has favoured venous dissemination.

Nevertheless, it is noteworthy that Batson (1942) himself contrasted lymph and venous blood flow and concluded that the flow within the vertebral venous system was such that 'no barrier exists at the midline'. If this is so, then a consistent ipsilateral localization of cephalic deposits should not be attributed to venous transportation. It seems, therefore, that lymphogenous metastasis should continue to receive our serious attention for, as I have argued elsewhere (Onuigbo, 1959), this mode of metastasis is in the main ipsilateral.

Hitherto, orthodox teaching, e.g. Cameron (1954), has been that 'blood invasion is indispensable if a tumour is to spread to distant parts'. Currently, however, research on the circulating cancer cell is revealing that up to 99% (Moore, Sandberg and Watne, 1959) of these cells apparently come to grief in the blood stream. The question ought to be posed and if possible answered by concerted efforts: What role does lymph play in transporting cancer cells to distant sites? We may be missing an important link in the chain of our knowledge of the mechanism of metastasis by largely ignoring lymphatic pathways. In particular, it is now a century since Virchow (1860) wrote concerning the 'very essential and important fact that the fibrin which circulates in lymph differs in certain respects from that contained in the blood'. Perhaps, such differences between blood and lymph may hold the key to our future advances in understanding cancer metastasis.

Summary

(1) Today, opinion is divided as to whether neuroblastomas show any tendency towards ipsilateral metastasis to the orbit and skull.

(2) A statistical study has, therefore, been made of the topographical distribution of the metastases in 132 neuroblastomas with cephalic involvement. One hundred and one cases were collected from the literature, 22 cases from The Hospital for Sick Children, Great Ormond Street, London, and nine from the Royal Hospital for Sick Children, Yorkhill, Glasgow.

(3) Eighty-six neuroblastomas exhibited an ipsilateral trend in their cephalic metastases, and only 46 displayed a contralateral trend. The difference in favour of ipsilateral metastasis is highly significant ($\chi^2 = 28{\cdot}223$, $p < 0{\cdot}001$).

(4) Ipsilateral preponderance of metastases is thought to be suggestive not of arterial or venous dissemination but of lymph-borne metastasis. Since current research suggests that very many of the circulating cancer cells apparently come to grief in the blood stream, there is need for concerted work on the fate of these cells in the lymph stream. It may well be that the role of the lymphatics in distant dispersal of cancer is underestimated.

I am grateful to my chief, Professor D. F. Cappell, to Dr. M. Bodian of The Hospital for Sick Children, Great Ormond Street, London, and Dr. A. M. Macdonald of the Royal Hospital for Sick Children, Glasgow, for the opportunity to carry out this survey.

References

Ackerman, L. V. and Regato, J. A. del (1947). *Cancer*, p. 787. Mosby, St. Louis.

Aisenstein, S. M. (1905). Beiträge z. Kasuistik der Nebennierentumoren im Kindesalter. Inaug. Diss. Zürich, 1905. Quoted by Tileston, W. and Wolbach, J. B. (1908).

Alyea, E. P. (1933). Medulloblastoma involving the kidney. *Sth. med. J. (Bgham, Ala.)*, **26**, 753.

Barden, R. P. (1943). The similarity of clinical and roentgen findings in children with Ewing's sarcoma (endothelial myeloma) and sympathetic neuroblastoma. *Amer. J. Roentgenol.*, **50**, 575.

Batson, O. V. (1940). The function of the vertebral veins and their rôle in the spread of metastases. *Ann. Surg.*, **112**, 138.

—— (1942). The rôle of the vertebral veins in metastatic processes. *Ann. intern. Med.*, **16**, 38.

Belt, E. (1959). In *Cancer: Diagnosis and Treatment*, ed. J. B. Field, p. 351. Churchill, London.

Bendixen, P. A. and Lamb, F. H. (1926). Malignant tumors of the adrenal in children with report of a case. *J. Lab. clin. Med.*, **12**, 130.

Blacklock, J. W. S. (1934). Neurogenic tumours of the sympathetic system in children. *J. Path. Bact.*, **39**, 27.

Bothman, L. and Blankstein, S. S. (1942). The eye in adrenal sympathicoblastoma (neuroblastoma). Importance of ocular findings, with first pathologic report of metastatic tumor in choroid. *Arch. Ophthal. (Chicago)*, **27**, 746.

Boyd, R. W. (1950). Adrenal neuroblastoma. *Canad. med. Ass. J.*, **63**, 153.

Boyd, W. (1926). Three tumors arising from neuroblasts. *Arch. Surg. (Chicago)*, **12**, 1031.

—— (1932). *A Text-Book of Pathology: An Introduction to Medicine*, p. 678. Kimpton, London.

—— (1958). *Pathology for the Physician*, 6th ed., p. 505. Kimpton, London.

Bruck, A. W. (1905). Ein Fall von kongenitalen Lebersarkom und Nebennierensarkom mit Metastasen. *Jahrb. f. Kinderheilk.*, **62**, 82. Quoted by Hutchinson, R. (1907).

Busfield, P. I. (1958). Neuroblastoma in orthopaedic practice. *J. Bone Jt Surg.*, **40B**, 47.

Cameron, G. R. (1954). The liver as a site and source of cancer. *Brit. med. J.*, **1**, 347.

Carter, W. E. (1921). Medullary malignancies of the suprarenal gland, with report of cases. *Amer. J. Dis. Child.*, **22**, 244.

Chaffey, W. C. (1885). Multiple sarcoma in a child. (Card specimen.) *Trans. path. Soc. Lond.*, **36**, 415.

Chont, L. K. (1941). Neuroblastoma and its roentgen diagnosis. Report of eight cases. *Amer. J. Roentgenol.*, **46**, 809.

Clark, W. C. (1939). Adrenal neuroblastoma, with particular reference to metastasis to the orbit. Report of a case and notes on two other cases. *Arch. Ophthal. (Chicago)*, **22**, 575.

Cohn, M. (1894). Primäres Nebennierensarkom bei einem neunmonatlichen Kind. *Berl. klin. Wschr.*, **31**, 226. Quoted by Hutchison (1907).

Cox, R. A. (1948). Proptosis due to neuroblastoma of the adrenal cortex (Hutchinson's syndrome). Report of a case. *Arch. Ophthal. (Chicago)*, **39**, 731.

Cust, N. (1937). Neuroblastoma of the adrenal, with massive metastases and purpura. *Med. J. Aust.*, **2**, 57.

Donnally, H. H., Rice, E. C., Jr. and Giddens, S. W. (1939). Neuroblastoma. Review and report of a case. *Med. Ann. D.C.*, **8**, 208.

Duke-Elder, Sir S. (1952). *Text-book of Ophthalmology*, vol. 5, p. 5618. Kimpton, London.

Fisher, Sir R. A. and Yates, F. (1957). *Statistical Tables*, 5th ed., pp. 2 and 45. Oliver and Boyd, Edinburgh.

Fleming, R. A. and Davidson, J. (1924). A case of neuroblastoma (neurocytoma). *Trans. med.-chir. Soc. Edinb.*, Session CIV (1924-1925), pp. 142-9.

Ford, F. R. (1945). *Diseases of the Nervous System in Infancy, Childhood and Adolescence*, 2nd ed., p. 858. Thomas, Springfield, Illinois.
Fresh, R. S. (1911). M.D. Thesis, (1910), Edinburgh University. On carcinoma originating in the suprarenal medulla in children. (See also *Quart. J. Med.*, **4**, 123.)
Gibson, T. E. (1927). The diagnosis of adrenal tumors. With classification of adrenal tumor syndromes, and report of cases. *J. Urol.* (*Baltimore*), **18**, 33.
Greenthal, R. M. and Epstein, E. (1939). Adrenal neuroblastoma. Report of a case. *Arch. Pediat.*, **56**, 561.
Greig, D. M. (1929). The cephalic metastases of suprarenal blastomata in children. *Edinb. med. J.*, **36**, 25.
Grogono, B. J. S. (1956). Neuroblastoma of the adrenal presenting with intraperitoneal haemorrhage. *Brit. J. Surg.*, **43**, 550.
Guibor, G. P. (1942). Adrenal neuroblastoma with orbital metastases. A case report with autopsy. *Amer. J. Ophthal.*, **25**, 387.
Gunby, P. C. (1920). Neuroblastoma sympathicum: report of one case. *Amer. J. med. Sci.*, **160**, 207.
Gupta, B. K. D. and Roy, S. (1957). Ocular metastases in Hutchison-Pepper syndrome. *A.M.A. Arch. Ophthal.* (*Chicago*), **57**, 821.
Hansen, P. B. (1953). Sympathicoblastoma of the adrenal medulla with osseous metastases. A report of three cases, including one surviving eleven years after roentgen therapy. *Acta radiol.* (*Stockh.*), **40**, 500.
Harrison, F. G., Warres, H. L. and Fust, J. A. (1950). Neuroblastoma involving the urinary tract. *J. Urol.* (*Baltimore*), **63**, 598.
Hartung, A. and Rubert, S. R. (1935). Roentgen aspects of sympathetic neuroblastoma; with report of two cases. *Radiology*, **24**, 607.
Henle, C-B. (1928). Roentgen findings in neuroblastoma. *Amer. J. Roentgenol.*, **20**, 414.
Holmes, G. W. and Dresser, R. (1928). Roentgenologic observations in neuroblastoma. *J. Amer. med. Ass.*, **91**, 1246.
Hutchison, R. (1907). On suprarenal sarcoma in children with metastases in the skull. *Quart. J. Med.*, **1**, 33.
Hyman, W. and Sztramski, G. A. (1955). Misdiagnosis of neuroblastoma. *N.Y. St. J. Med.*, **55**, 1344.
Karsner, H. T. (1942). Distribution of metastases of neuroblastoma of the adrenal. *Trans. Ass. Amer. Phycns*, **57**, 209.
Kato, K. and Wachter, H. E. (1938). Adrenal sympathicoblastoma in children, with special reference to biopsy of sternal marrow and of metastatic nodule in skull. *J. Pediat.*, **12**, 449.
Klein, J. (1932). Neuroblastoma of the adrenal with multiple metastases. *Amer. J. med. Sci.*, **184**, 491.
Kuhn, H. S. (1939). Adrenal neuroblastoma and its ocular symptoms: a case report with autopsy. *Amer. J. Ophthal.*, **22**, 642.
Law, F. W. (1932). Adrenal neuroblastoma: a case with metastases causing blindness. *Lancet*, **2**, 1101.
Leach, W. (1957). A case of neuroblastoma. *Postgrad. med. J.*, **33**, 561.
Lederer, M. (1926). Neuroblastoma of adrenal gland (Hutchinson type); report of a case. *J. Cancer Res.*, **10**, 377.
Lewis, D. and Geschickter, C. F. (1934). Tumors of the sympathetic nervous system. Neuroblastoma, paraganglioma, ganglioneuroma. *Arch. Surg.* (*Chicago*), **28**, 16.
Loomis, E. A. and Loomis, G. L. (1949). Adrenal sympathoblastoma (neuroblastoma). *Minn. Med.*, **32**, 606.
Lucas, P. J. (1940). Neuroblastoma with origin in the celiac ganglion. *Med. Tms* (*N.Y.*), **68**, 411.
MacCarty, W. C. (1905). *Berl. klin. Wschr.*, **42**, 115, 2nd part, Festnummer f. Ewald, p. 115. Quoted by Tileston, W. and Wolbach, S. B. (1908).
Maclean, R. N. (1959). Hypercalcemia related to neuroblastoma. *Arch. Pediat.*, **76**, 64.
Mann, H. C. (1909). Primary sarcoma of the adrenal. *Proc. roy. Soc. Med.*, 2 (Sect. Dis. Children), 160.
Moore, G. E., Sandberg, A. A. and Watne, A. L. (1959). The spread of malignant cells: a review. *Univ. Mich. med. Bull.*, **25**, 191.
Neale, A. V. (1954). In *Diseases of Infancy and Childhood*, ed. Sir L. Parsons, S. Barling and C. G. Parsons, 2nd ed., vol. 1, p. 481. Oxford University Press, London.
Oberkircher, O. J., Staubitz, W. J. and Parmenter, F. J. (1953). A clinical study of neuroblastoma. *J. Pediat.*, **43**, 177.
Ogden, O. W. and Mathews, P. (1906). A case of sarcoma with secondary intra-cranial growths in a child of five. *Brit. J. Child. Dis.*, **3**, 394.
Onuigbo, W. I. B. (1959). Lung cancer—metastatic theory and surgical practice. *J. thorac. Surg.*, **37**, 771.
Pack, G. T., Horning, E. D. and Ariel, I. M. (1952). Neuroblastoma (sympathicoblastoma). With an analysis of 14 cases and a survey of the literature. *J. Neuropath. exp. Neurol.*, **11**, 235.
Pepper, W. (1901). A study of congenital sarcoma of the liver and suprarenal. With report of a case. *Amer. J. med. Sci.*, **121**, 287.
Pi, C. C. (1944). Adrenal neuroblastoma. Report of a case. *Chin. med. J.*, **62A**, 167.
Platt, A. H. (1911). A case of sarcoma of the supra-renal body, with secondary involvement of the vault of the skull and orbits. *Ophthalmoscope* (*Lond.*), **9**, 107.
Poore, T. N. (1949). M.S. (Surgery) Thesis, University of Minnesota. Abdominal neuroblastoma, p. 56.
——, Dockerty, M. B., Kennedy, R. L. J. and Walters, W. (1951). Abdominal neuroblastomas. *Surg. Clin. N. Amer.*, **31**, 1121.
Redman, J. L., Agerty, H. A., Barthmaier, O. F. and Fisher, H. R. (1938). Adrenal neuroblastoma. Report of a case and review of the literature. *Amer. J. Dis. Child.*, **56**, 1097.
Reiquam, C. W., Beatty, E. C., Jr. and Allen, R. P. (1956). Neuroblastomas in infancy and childhood. *Ibid.*, **91**, 588.
Riad Bey, M. (1942). Metastatic neuroblastoma of the orbit. *Bull. ophthal. Soc. Egypt*, **35**, 81.
Rosendal, T. (1942). Two cases of sympathicoblastoma of the suprarenal gland with metastases to the cranium and the tubular bones. *Acta radiol.* (*Stockh.*), **23**, 462.
Schroder, J. R. (1949). Neuroblastoma. Report of a case. *Wis. med. J.*, **48**, 1000.
Seaman, W. B. and Eagleton, M. D. (1957). Radiation therapy of neuroblastoma. *Radiology*, **68**, 1.
Shaffer, R. N. (1947). Neuroblastoma of the adrenal with orbital metastases. Report of five cases with autopsy findings. *Amer. J. Ophthal.*, **30**, 733.
Sladden, R. A. (1953). D.M. Thesis, Oxford University. The natural history of the malignant embryonic tumours of the sympathetic nervous system, p. 85.
Steward, J. K. (1958). In *Modern Trends in Paediatrics*, 2nd series, ed. A. Holzel and J. P. M. Tizard, p. 165. Butterworth, London.
Stowens, D. (1959). *Pediatric Pathology*, p. 347. Bailliere, Tindall and Cox, London.
Sturtevant, C. N. and Kelly, T. C. (1927). Neurocytoma of the left suprarenal gland with metastases to the liver, skull and bones. *Amer. J. Dis. Child.*, **33**, 590.
Targett, J. H. (1888). Multiple sarcomata of skull, ribs and glands. (Card specimen.) *Trans. path. Soc. Lond.*, **39**, 306.
Thompson, R. M. (1942). Neuroblastoma (sympathoblastoma or neurocytoma) of the suprarenal medulla: report of three cases. *Ann. intern. Med.*, **16**, 1206.
Tidswell, F. and Sear, H. R. (1933). Neuroblastoma: Experiences at the Royal Alexandra Hospital for Children, Sydney. *Aust. N.Z. J. Surg.*, **2**, 360.
Tileston, W. and Wolbach, S. B. (1908). Primary tumors of the adrenal gland in children. Report of a case of simultaneous sarcoma of the adrenal gland and of the cranium, with exophthalmos. *Amer. J. med. Sci.*, **135**, 871.
Trotter, R. F. and Winchell, W. H. (1954). Neuroblastoma. *U.S. armed Forces med. J.*, **5**, 1820.
Virchow, R. (1860). *Cellular Pathology*, translated by F. Chance, pp. 158-9. Churchill, London.
Wessely (1919). Quoted by Scott, E., Oliver, M. G. and Oliver, M. H. (1933). Sympathetic tumours of the adrenal medulla; with report of four cases. *Amer. J. Cancer*, **17**, 396.
Willis, R. A. (1952). *The Spread of Tumours in the Human Body*, 2nd ed., p. 104. Butterworth, London.
Wollstein, M. (1928). Neuroblastoma of the adrenal in young children. *Surg. Gynec. Obstet.*, **46**, 774.

TUBERCULOSIS IN B.C.G. VACCINATED CHILDREN IN SINGAPORE

BY

FREDA M. PAUL

From the Paediatric Unit, the General Hospital, Singapore

(RECEIVED FOR PUBLICATION JANUARY 11, 1961)

B.C.G. vaccination is generally considered a useful adjunct in the fight against tuberculosis. Although it does not necessarily completely protect the subject from contracting tuberculosis, it probably prevents the more severe forms of the disease such as tuberculous meningitis, miliary tuberculosis and the severe pulmonary forms of the disease. To assess the real value of B.C.G. vaccination, it is necessary to isolate the subject from contacts, until the conversion of the Mantoux tuberculin test proves effective vaccination. That B.C.G. vaccination is not completely protective against the development of tuberculous meningitis has been proved by Lorber and Menneer (1959), but that it does have considerable protective effect on the development of tuberculosis has been shown by the recent trials carried out by the Medical Research Council (1959) where the incidence of tuberculosis in the B.C.G. vaccinated group was 0·38 per 1,000 compared with 2·29 per 1,000 among those in the tuberculin negative unvaccinated group who were admitted concurrently. This represents a reduction attributable to vaccination of 83%.

Field trials of B.C.G. have so often been open to criticism for one reason or another, but what we wanted to find out was the effect of mass campaigns where isolation of the patient was not practical.

In Singapore, the U.N.I.C.E.F./W.H.O. team initiated B.C.G. vaccination in June 1951. Up to the end of 1953, a total of 35,894 people were inoculated, of whom only 1,607 were newborn. In 1957, a mass B.C.G. campaign amongst the newborn was started at the main Kandang Kerbau Maternity Hospital. Almost 50% of the babies born on the island are delivered at this Hospital.

Table 1 shows the number of cases vaccinated each year with the total number of births from Singapore.

The number of cases of tuberculous meningitis admitted to the Paediatric Unit, General Hospital, is shown in Table 2.

TABLE 2

NUMBER OF CASES OF TUBERCULOUS MENINGITIS ADMITTED IN PAEDIATRIC UNIT, GENERAL HOSPITAL, SINGAPORE

Year	No. of Cases	Mortality (%)	Total Number of Admissions
1955	112	60·7	No. not available
1956	106	44·3	6,473
1957	60	45	7,217
1958	52	30·7	9,697
1959	45	28·9	10,517
1960 (from Jan. to Sept.)	36	16·6	8,400

The Paediatric Unit admits children up to 10 years of age, and about 90% of children requiring medical treatment are admitted here. The figures, therefore, give a good idea of the pattern of disease in children on the island. It will be seen that the incidence of tuberculous meningitis dropped considerably in 1957. Factors which helped to bring this about were better adult control of tuberculosis, a mass x-ray campaign and the introduction of B.C.G. vaccination.

Of particular interest, however, were 14 cases of

TABLE 1

	1956	1957	1958	1959	1960 (Jan. to June)
Number of B.C.G. vaccinations at Kandang Kerbau Hospital ..	—	22,168	23,889	28,283	15,072
Number of B.C.G. vaccinations at Infant Welfare Clinic:					
(*a*) Urban (commenced July 1958)	—	—	2,904	5,936	2,815
(*b*) Rural (commenced July 1956)	221	517	2,866	4,078	2,597
Number of births in Singapore	60,892	62,685	63,572	62,464	29,844

TABLE 3

AGE, INCIDENCE AND SEX DISTRIBUTION OF 14 CASES OF TUBERCULOUS MENINGITIS

Case No.	Age yrs	Age mths	Sex	Mantoux Tests with Old Tuberculin
1	1		Male	1/1,000 dilution positive
2	2		Female	1/100 ,, positive
3	1	4	Female	1/1,000 ,, positive
4	2		Female	1/1,000 ,, positive
5	2		Female	1/1,000 ,, positive
6	1	4	Female	1/1,000 ,, positive
7		7	Female	1/100 ,, positive
8	2		Female	1/100 ,, positive
9		7	Male	1/1,000 ,, positive
10		10	Male	1/1,000 and 1/100 negative
11	1		Male	1/100 dilution positive
12	2		Male	1/1,000 ,, positive
13	2		Male	1/100 ,, negative
14		8	Female	1/100 ,, negative

tuberculous meningitis (Table 3) and two cases of severe pulmonary tuberculosis in children, who had received B.C.G. vaccination at birth, and had been admitted to the Paediatric Unit, the General Hospital, during the years 1958, 1959 and 1960.

It will be noted that six of these children were in the 2-year age period, four were 1 year old, and four under the age of 1 year. The youngest case was 7 months old. The concentration of the disease under the age of 2 years shows the poor resistance of these children in this young age group in spite of immunization.

There was no striking difference in the sex incidence.

Investigations

B.C.G. In all these cases B.C.G. had been given at birth at the Kandang Kerbau Maternity Unit. The presence of a scar was noted in all cases by the examining doctor. In three children Mantoux testing was done three months after the vaccination by the B.C.G. team and all three were reported to be positive.

It is not known whether the rest of the children had been tuberculin converted, but from an original survey in 1957 it is known that 97% of B.C.G. vaccinated newborn infants in Singapore had a Mantoux conversion at 3 months of age.

Mantoux Tests. Thirteen of the 14 cases had a positive Mantoux test when tested in the wards after admission (seven were positive to 1 in 1,000 old tuberculin and five to 1 in 100 old tuberculin). Case 10 had a negative Mantoux test in the ward, but was reported to have had a positive Mantoux test three months after the B.C.G. vaccination at birth. This child developed internal hydrocephalus and eventually died. It is well known that in a severe form of the disease the Mantoux test will be negative, and this probably accounts for the negative reaction.

The striking feature of this group of cases of tuberculous meningitis occurring in children who had received B.C.G. at birth in contrast to those who had no B.C.G. was the very short history, and the quick recovery and return of the cerebrospinal fluid to normal. The short history of these cases made it difficult to distinguish them from Japanese B encephalitis that occurs so commonly here. Table 4 shows the average length of history in each case and the main symptoms.

It will be noted that 12 of the 14 cases gave a history of symptoms lasting 10 days or less than 10 days.

Fever was present in all cases, fits in 64%, vomiting in 57%, drowsiness in 86%, constipation in 36% and paralysis in 14% of the cases. These were the symptoms described by the parents on admission of the children.

TABLE 4

LENGTH OF HISTORY AND MAIN SYMPTOMS

Case No.	Average Length of History	Symptoms					
		Fever	Fits	Vomiting	Drowsiness	Paralysis	Constipation
1	3 weeks	+	+	−	+	−	+
2	1 week	+	−	+	+	−	−
3	3 days	+	+	+	+	+	−
4	10 days	+	−	+	+	+	+
5	10 days	+	+	+	−	−	+
6	2 days	+	+	−	+	−	−
7	1 week	+	−	+	+	−	+
8	1 week	+	−	+	+	−	−
9	1 month	+	+	−	+	−	+
10	4 days	+	+	+	−	−	−
11	3 days	+	+	−	+	−	−
12	5 days	+	+	−	+	−	−
13	7 days	+	−	−	+	−	−
14	2 days	+	+	+	+	−	−

+ Present; − Absent.

TABLE 5
SIGNS PRESENT AT INITIAL EXAMINATION

Case No.	Coma	Rigidity of Limbs	Neck Rigidity	Paralysis Limbs	Facial Paralysis	Papilloedema	Abnormal Movement
1	+	+	+	−	−	−	−
2	++	+	−	+	−	−	+
3	+	+	−	+	+	−	−
4	+	−	−	+	−	−	−
5	+	+	+	−	−	−	−
6	+	−	+	+	−	−	−
7	+	+	−	−	−	−	+
8	++	+	−	−	−	+	+
9	+	+	+	−	−	−	−
10	+++	+	−	−	−	+	−
11	+	−	+	−	−	−	−
12	+	−	+	−	−	−	−
13	+	+	+	+	−	−	−
14	+	+	+	+	−	−	−

+ Present; ++ Moderate; +++ Deep; — Absent

Case 4 was admitted with left hemiparesis and fever and did not look too ill at the onset of admission. The parents refused medical treatment and took the child home against medical advice on the day of admission. He was readmitted in coma four days later and died the next day. Autopsy showed miliary tuberculosis with tuberculosis of the meninges.

Case 14 is interesting because of the close resemblance to a case of febrile fits. He had a normal cerebrospinal fluid on admission, but was readmitted two days later in coma with cerebrospinal fluid changes. He eventually responded to anti-tuberculous treatment.

The temperature returned to normal by the end of the second week and improvement clinically and serologically became evident by the end of the second week.

Physical Signs. As the cerebrospinal fluid of these cases on direct smear and on culture did not show the tubercle bacillus, the clinical picture of the child, together with the radiological findings and the biochemical findings of the cerebrospinal fluid were vitally important.

Table 5 illustrates the main signs present in each case on initial examination.

All the children were in varying degrees of coma. The vacant stare so characteristic of tuberculous meningitis was present in most of the cases. Rigidity of the limbs was present in 71%, while flaccidity of the limbs in the form of hemiparesis was present in 36% of cases. Two children had papilloedema, one due to the development of internal hydrocephalus. This child came in with a four-day history of fever and fits. The cerebrospinal fluid showed a total protein of 200 mg. % on admission. The child was comatose throughout the four months' stay in hospital. In spite of intrathecal prednisolone the child did not respond. Fig. 1 shows the air encephalogram indicating the dilated lateral ventricles.

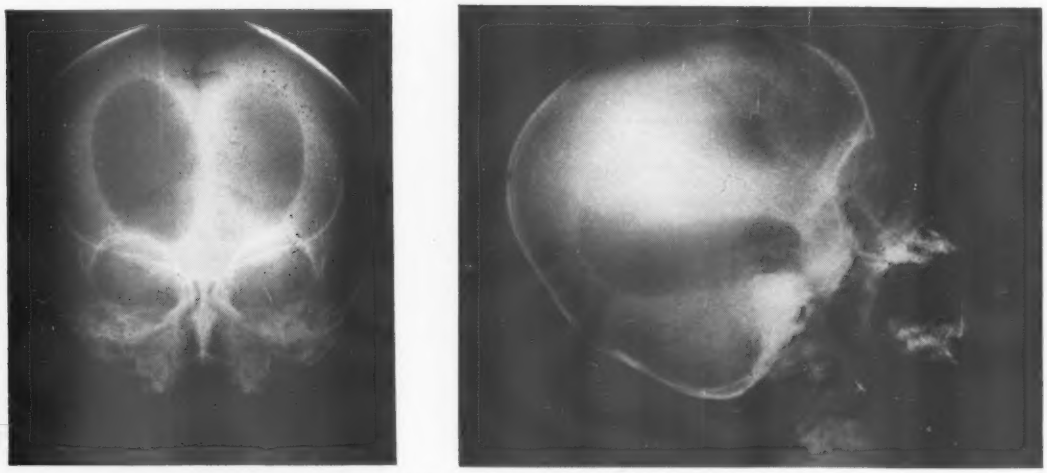


FIG. 1.—Air encephalogram indicating the dilated lateral ventricles.

TABLE 6
THE CEREBROSPINAL FLUID CHANGES

Case No.	Cell Count	Total Protein (mg./100 ml.)	Globulin	Sugar (mg./100 ml.)	Chloride (mg./100 ml.)	Lympho-cytes	Organisms	Date
1	40	50	Trace	40	700	Few	Nil	9.9.58
	2	30	Nil	+	670	Few	Nil	30.9.58
2	20	120	+	20	660	+	−	13.11.58
	4	70	+	40	680	+	−	26.11.58
	3	40	+	48	700	+	−	24.12.58
3	20	30	−	20	660	+	−	31.5.58
	1	20	Nil	+	720	−	−	16.6.58
4	60	50	+	40	650	Few	−	14.1.59 died next day
5	120	90	+	20	650	+	−	9.5.59
	15	50	Trace	50	700	+	−	16.5.59
	5	40	Trace	40	700	+	−	22.5.59
6	30	90	+	33	600	+	−	24.10.57
	4	60	+	54	680	+	−	20.1.58
7	500	50	+	43	690	+	−	27.9.59
	2	50	+	55	720	+	−	19.10.59
8	20	120	+	20	660	Few	−	13.11.58
	4	70	+	64	680	Few	−	26.11.58
9	140	160	+	45	680	+	−	23.5.58
	20	100	+	43	660	−	−	30.6.58
	8	30	+	60	700	−	−	20.8.58
10	480	140	Nil	42	650	++	−	27.11.57
	5	60	Trace	50	700	−	−	7.12.57
	1	40	Trace	50	700	−	−	16.12.57
11	20	40	Nil	43	740	Few	−	30.12.59
	2	70	+	50	740	Few	−	7.1.60
12	150	100	+	50	—	+	−	9.9.59
	4	30	−	40	—	+	−	8.11.59
13	576	160	+	12	—	++	−	13.7.60 under treatment
14	2	40	Nil	+	660	+	−	23.2.60
	40	60	+	50	700	+	−	25.2.60
	8	60	Trace	55	700	+	−	30.3.60

Radiological Evidence. Radiologically there was evidence of a primary infection in all except one case. In nine cases there were increased hilar markings with evidence of calcification on later radiographs, while two cases had widening of the superior mediastinum and two others had consolidation of the right middle lobe. Case 1 had miliary tuberculosis of the lungs.

Deaths. There were three deaths among the 14 children. Case 3 was a 2-year-old Sikh child who was treated as a case of tuberculous meningitis, recovered and was discharged. She was followed as an out-patient and three months later was admitted with severe hyperpyrexia and fits after an attack of tonsillitis; she died.

The parents of Case 4 refused to admit the child to hospital. She was admitted in coma four days later and eventually died. Autopsy showed an indurated mass at the apical portion of the right lower lobe with miliary tubercles scattered throughout both lungs. The right tracheobronchial lymph nodes were enlarged and matted. The liver and spleen were studded with tubercles and the base of the brain had a fibrinous exudate with miliary tubercles. Case 10 was admitted in a comatose state and did not improve in spite of treatment. She developed an internal hydrocephalus and died six months after admission. There was no autopsy.

Cerebrospinal Fluid Changes. The mean of the first specimens of the cerebrospinal fluid taken within 12 hours of admission were, cells: 20-500/c.mm. (mean: 40/c.mm.); total protein: 50-160 mg./100 ml. (mean: 100 mg./100 ml.); glucose: 12-50 mg./100 ml. (mean: 40 mg./100 ml.).

The cells were predominantly lymphocytes. The cerebrospinal fluid in tuberculous meningitis in the non-vaccinated group normally takes one to three months to return to normal. In some cases where the protein is high this may take six months. It was observed that in the B.C.G. vaccinated group the cerebrospinal fluid returned to normal much sooner.

Table 6 shows the initial cerebrospinal fluid changes and the time taken to return to normal.

Contacts. With the aid of the almoner and by interview with the parents it was found that six of the children had been in contact with adults suffering from pulmonary tuberculosis. Case 3 had been in contact with a Chinese neighbour suffering from pulmonary tuberculosis. The father of Case 5 had pulmonary tuberculosis. Case 6 had a tuberculous mother who was under treatment

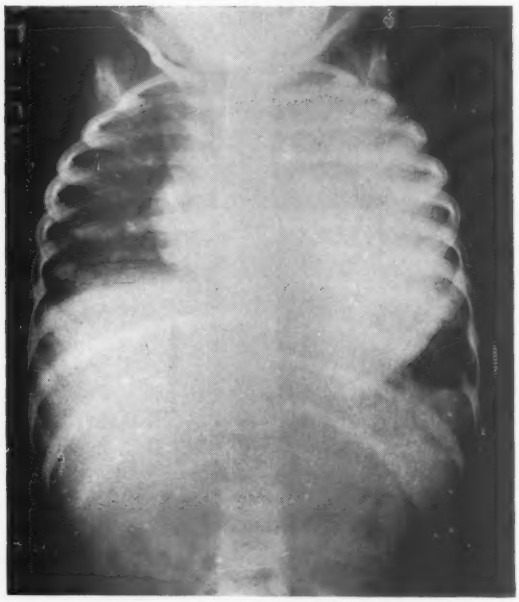


FIG. 2.—Radiograph showing left pleural effusion and miliary mottlings of the right lung.

for tuberculosis. The almoner's report on Case 9 stated that 25 to 30 people were living in the same house with the patient. Out of these, two were known to have pulmonary tuberculosis. One occupant had recently died of pulmonary tuberculosis, while the second occupant was the patient's aunt who attended the tuberculous hospital for

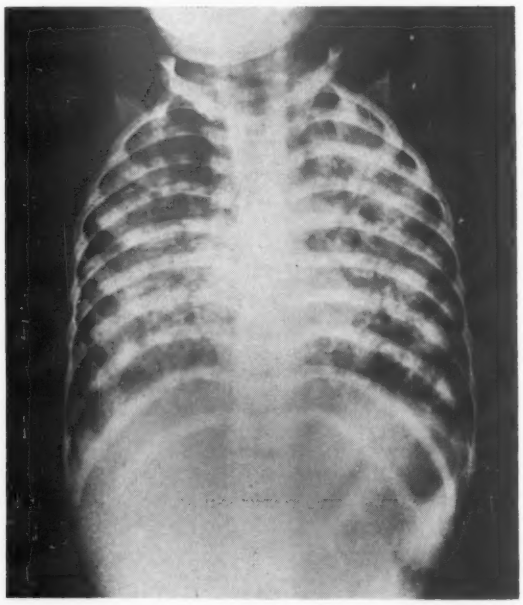


FIG. 3.—Radiograph showing tuberculous bronchopneumonia.

treatment. This case was the youngest child in this series, aged 7 months, who had been given B.C.G. at birth and was known to be tuberculin positive three months later. Overcrowding and inadequate facilities for isolation of children from contact with tuberculous parents and relatives are a problem here.

Sequelae. These children have not been followed up long enough to estimate their mental state. Physically, three had hemiparesis and one developed internal hydrocephalus. Case 7 is mentally backward. Three children were reported by the parents to be extremely mischievous and to have temper tantrums.

Case Reports

The following two cases are interesting in that they represent two fulminating types of pulmonary tuberculosis developing in children in spite of having been B.C.G. vaccinated at birth.

Case 1. A Malay child, aged 4 years, was admitted to the Paediatric Unit because of low-grade evening fever for five months, cough for three months, and loss of weight over a period of five months. She was the second child in a family of three and was given B.C.G. at birth.

On clinical examination the child was emaciated with a temperature of 101° F., and breathless with poor movement of the left side of the chest. A pleural effusion was suspected clinically because the percussion note was dull and the air entry was poor. The liver was enlarged, being palpable one finger breadth below the costal margin. The right fundus showed choroidal tubercles. Radiologically there was a left pleural effusion with miliary mottling of the right lung (Fig. 2.)

Mantoux test to old tuberculin in the dilution of 1/1,000 and 1/100 was negative. The sputum, however, showed acid-fast bacilli on direct smear. A lumbar puncture was done to exclude tuberculous meningitis, but the cerebrospinal fluid was found to be normal serologically. In this case the contact was an aunt who was living in the same house and who had pulmonary tuberculosis for which she was under treatment. After a week's stay in hospital the parents took the child home, against medical advice, and she is now attending an out-patient clinic for streptomycin injections.

Case 2. A 15-month-old Chinese child was admitted in August 1960, with a three-month history of low-grade fever, associated with cough. He was a normal baby at birth, given B.C.G. at the Kandang Kerbau Maternity Hospital and had developed normally till three months before admission.

On examination he was ill, emaciated, extremely pale and breathless. On clinical examination there was consolidation of the left upper lobe with coarse râles over both lungs. The abdomen was scaphoid with a liver two finger breadths below the costal margin, and

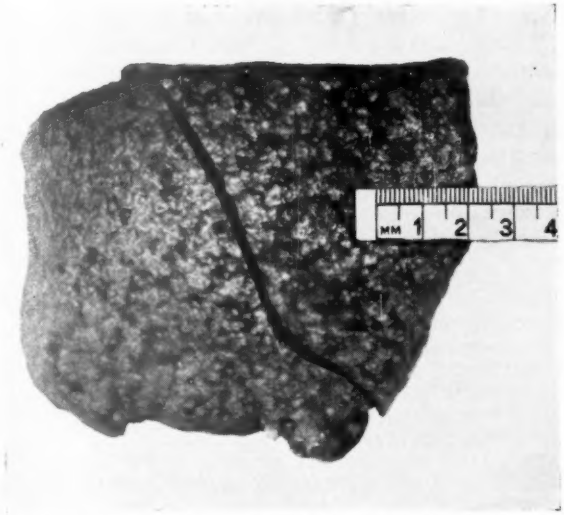


FIG. 4.—Autopsy specimen of the lungs. Note that the left lung is riddled with patchy coarse areas of tuberculosis.

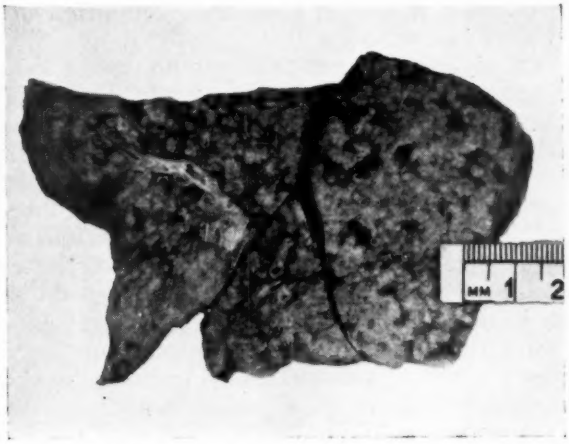


FIG. 5.—The left lung with the bronchus of the left lower lobe infiltrated with tuberculous granulation tissue.

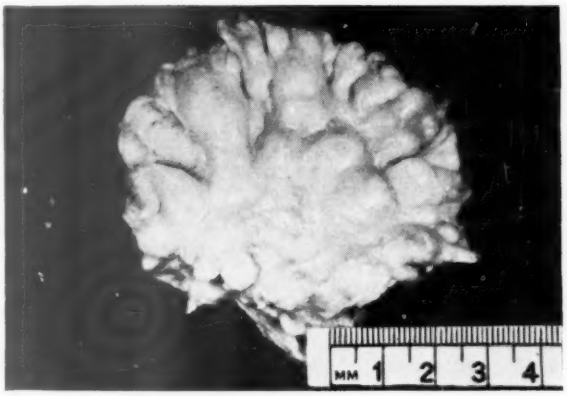


FIG. 6.—Autopsy specimen of the enlarged mesenteric glands.

FIG. 7.—Cross-section of the enlarged lymph nodes showing caseation.

enlarged mesenteric glands were palpable. There were no neurological signs. The cerebrospinal fluid was normal, the B.S.R. was only 6 mm. and the Mantoux test was negative. Radiologically there was coarse mottling of both lungs, consistent with tuberculous bronchopneumonia (Fig. 3).

In this case the contact was an uncle, who was being followed up at the T.B. Hospital for pulmonary tuberculosis, and lived in the same room as the rest of the patient's family, which included seven other children.

This child died three days after admission. Autopsy revealed bronchogenic tuberculosis with enlarged cervical and mesenteric lymph nodes (Figs. 4-7).

Discussion

It has been demonstrated many times that B.C.G. vaccination can prevent tuberculosis. For example, Aronson, Aronson and Taylor (1958) vaccinated 1,557 American Indian children 20 years ago and left 1,457 as controls. The incidence of tuberculosis in that community was high at the time these vaccinations were done. Twenty years later they found that 6·7% of the vaccinated group had died, tuberculosis being responsible for 0·8% of the deaths. Of the controls 10·4% died, tuberculosis accounting for 4·7% of cases. Hyge (1947) observed an epidemic of tuberculosis in a school in Denmark. Of 94 tuberculin negative children who were exposed to an infectious school teacher, 41 developed tuberculosis; whereas of the 106 B.C.G. vaccinated children who were exposed to the same infection, only two developed the disease.

Lorber and Menneer (1959) reported a case of a 4-month-old infant who contracted tuberculosis when contact was resumed with her tuberculous

grandfather in spite of a successful conversion after B.C.G. vaccination.

In this country there have been no reports so far about the long-term effectiveness of B.C.G. vaccination in contacts. The incidence of childhood tuberculosis has dropped in this country and the introduction of B.C.G. has no doubt played a great part in the reduction. But the 14 cases of tuberculous meningitis and two cases of pulmonary tuberculosis in B.C.G. vaccinated children reported above are interesting in that they show that B.C.G. does not provide complete immunity.

In three of the 14 cases of tuberculous meningitis reported above, Mantoux tests three months after the vaccination of B.C.G. at birth were reported to be positive. Two of the three cases had relatives with tuberculosis living in the same room or house. This further proves the point that even after Mantoux conversion, the child has no absolute immunity from the disease unless protection from repeated exposure to the tuberculous subject is exercised. However, it is interesting to observe the short length of history of symptoms given in this group of B.C.G. vaccinated children developing tuberculous meningitis and the rather rapid return of the cerebrospinal fluid to normal.

Summary

Fourteen cases of tuberculous meningitis and two cases of pulmonary tuberculosis in B.C.G. vaccinated children are reported. Their symptoms, clinical features, cerebrospinal fluid changes, and progress are discussed. Considering the large number of children who are being vaccinated with B.C.G. in Singapore and the small number that develop tuberculosis, it can be concluded that B.C.G. vaccination during the neonatal period provides considerable if not absolute immunity.

I wish to thank Dr. C. E. Field, head of the Paediatric Unit, General Hospital, Singapore, for her advice, encouragement and help in this paper; Dr. Quah Quee Guan and Dr. Wong Hock Boon for permission to make use of patients in their unit; Dr. Ho Kok Kheong for the autopsy reports, and to Dr. Wong Hin Sung for supplying statistics on B.C.G. vaccination in Singapore. I am also indebted to Mr. Ho Tat Seng and to Mr. Naplon for the photographs. My thanks go to the Director of Medical Services, Singapore, for permission to publish this paper.

References

"Annual report of the Medical Department, 1952." Colony o Singapore (1953). p. 116. Government Printing Office, Singapore.

Aronson, J. D., Aronson, C. F. and Taylor, H. C. (1958). A twenty-year appraisal of B.C.G. vaccination in the control of tuberculosis. *A.M.A. Arch. intern. Med.*, **101**, 881.

Hyge, T. V. (1947). Epidemic of tuberculosis in state school, with observation period of about 3 years. *Acta tuberc. scand.*, **21**, 1.

Lorber, J. and Menneer, P. C. (1959). Long-term effectiveness of B.C.G. vaccination of infants in close contact with infectious tuberculosis. *Brit. med. J.*, **1**, 1430.

Medical Research Council (1959). B.C.G. and vole bacillus vaccines in the prevention of tuberculosis in adolescents. *Ibid.*, **2**, 379.

STUDIES IN THE PHYSIOLOGY OF SWEATING IN CYSTIC FIBROSIS

II: ELEVATED NIGHT SWEATING RATES*

BY

MAARTEN S. SIBINGA and GIULIO J. BARBERO

From the Children's Hospital of Philadelphia and Department of Pediatrics, School of Medicine, University of Pennsylvania

(RECEIVED FOR PUBLICATION FEBRUARY 27, 1961)

Since the discovery of high sodium chloride in the sweat of children with cystic fibrosis by di Sant' Agnese and others, many investigators have established this abnormality as a consistent finding (di Sant'Agnese, Darling, Perera and Shea, 1953; Shwachman, Leubner and Catzel, 1955; Sibinga and Barbero, 1961). A number of these reports have described a normal sweating rate in patients with cystic fibrosis (Gochberg and Cooke, 1956; Vink, 1957) when sweat was collected under thermal stimulation (di Sant'Agnese, Darling and Perera, 1953). Physicians and mothers, however, have frequently noted that children with cystic fibrosis sweat more profusely than other children. Parents describe multiple changes of bed clothing at night because of this profuse sweating. This apparent contradiction seemed to warrant investigation of spontaneous sweating as contrasted to the previously studied thermal and drug-induced sweating. This different approach to the physiological process of sweating might reveal abnormalities in threshold and sensitivity of the secretory mechanism.

Method

Collections of sweat on patients with cystic fibrosis and normal children of similar size were done simultaneously as follows: A round aluminium collection chamber of 2·5 cm. diameter (Schwartz, Thaysen and Dole, 1953) was glued on the skin between the scapulae. A number of pre-weighed discs of filter paper were inserted and sealed in the collection chamber, which was made airtight with a special cover. The apparatus was strapped in place with tape. By changing the filter paper at one- or two-hour intervals an accurate picture of the amount (as determined by weight) of sweat secreted was obtained. No extraneous stimulation was used. The environmental temperature was between 75° and 95° F. and relative humidity was between 80 and 95%.

Results

Fig. 1 shows the sweating rates of a child with cystic fibrosis and a normal child of equal weight (ages 4 years and 2 years 9 months) over a two-day period. Activity and temperature were accurately recorded. This experiment was continued over five days, and the pattern of sweating was identical from day to day. During the day the sweating rate in the normal child was greater than in the patient with cystic fibrosis. These differences were closely related to healthy physical activity. During the night after going to sleep, however, the sweating rate of the patient with cystic fibrosis invariably surpassed that of the normal child.

The periods during which the sweating rate of the cystic fibrosis patient exceeded that of the normal child are listed in Table 1. Similar trends in the 24-hour sweating pattern were observed on two other patients with cystic fibrosis during a number of days and compared with two control children.

These observations prompted an investigation of night sweating rates between 11 p.m. and 7 a.m. The total amounts collected at the same time on

TABLE 1

QUANTITIES OF SWEAT COLLECTED IN PATIENT WITH CYSTIC FIBROSIS AND CONTROL CHILD ON SUBSEQUENT DAYS

Days	Time p.m.	Time a.m.	Quantities of Sweat: Cystic Fibrosis Case (mg.)	Quantities of Sweat: Normal Case (mg.)
1	11.30	until 8	714	381
2	11	,, 5	120	68
3	10	,, 10	394	83
4	10	,, 10	491	68
5	10	,, 8	177	26

* This Study was supported by grants from the Lee Graub Memorial Fund and the National Institute of Allergy and Infectious Diseases, Public Health Service.

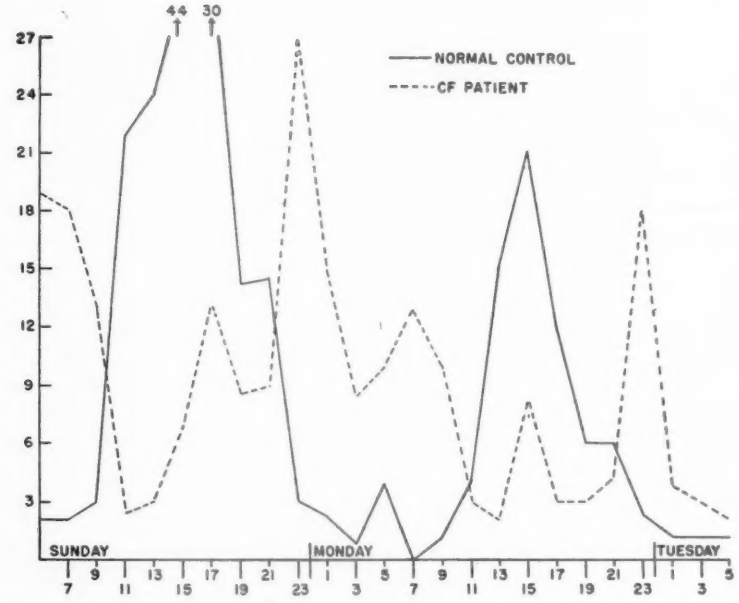


FIG.—Sweating rates of a child with cystic fibrosis and a normal child of equal weight over a two-day period.

seven cystic fibrosis patients and seven control subjects are shown in Table 2. The difference is highly significant statistically. The sodium concentrations of the spontaneous sweat showed a marked elevation in the patients with cystic fibrosis compared with the control children. However, the ranges of concentration of sodium in spontaneous sweat were 5-25 mEq/litre in patients with cystic fibrosis and 0-5 mEq/litre for the control children. The presence of very marked differences in concentration between subsequent samples in the patients with cystic fibrosis distinguished the two groups. The sodium concentration of the spontaneous sweat of the control children varied within a few mEq/litre when no marked differences in sweating rate were present, while the patients with cystic fibrosis frequently exhibited concentration differences of 10-15 mEq/litre in subsequent samples.

TABLE 2
NIGHT SWEAT SIMULTANEOUSLY COLLECTED OVER EIGHT-HOUR PERIODS

Cystic Fibrosis Patients (mg.)	Controls (mg.)
943	28
1,482	36
1,022	28
1,268	36
232	60
851	214
1,348	475

Discussion

In studying sweating rates one must distinguish carefully between the findings in different age groups. Many perfectly healthy young children will exhibit night sweating to a certain degree, while in adults this phenomenon seems more closely related to pathological conditions. Some of the control children in this study were showing obvious night sweating, and were selected for that reason.

The significantly increased rate of sweating of the patients with cystic fibrosis measured during the night in these experiments can be related to certain other observations. It has been known for a long time that various pulmonary diseases, specifically tuberculosis, are associated with night sweating. This is frequently interpreted as a sign of a low grade fever. It is also stated to occur with fever in advanced bronchiectasis (Harrison, Adams, Bennett, Resnik, Thorn and Wintrobe, 1958) and many other pulmonary diseases (Cecil and Loeb, 1959). The patients with cystic fibrosis investigated in this study did not exhibit any fever, neither was there any sign of rickets which may be accompanied by night sweating. Increased heat production due to the laborious respirations might well result in sweating; however, a marked increase in sweating rate was observed during the night in our patients with cystic fibrosis when the respiratory requirements were less rather than increased. The markedly increased basal metabolic rate in acute respiratory failure does not result in sweating (Harrison *et al.*, 1958), and some of our patients have sweated less in extreme respiratory insufficiency. Again no explanation for the increase during the night is found.

Congenital cardiac disease has been associated with night sweating and is said to disappear after cardiac surgery. Cyanosis is a feature in both cardiac disease and cystic fibrosis; however, two of the patients with cystic fibrosis were mild cases, one of whom had no respiratory involvement. Hyponatraemia may result in increased sweating rate (Amatruda and Welt, 1953). Blood sodium levels determined on several of the patients were normal and all cystic fibrosis patients were on supplementary salt intake. This last factor is not considered to be the cause of the observed difference in sweating rate. The mechanism for the sweating

that occurs with peripheral vascular collapse is not established with certainty and like many of the earlier examples have been classified as neuro-vegetative reactions. Kuno (1956) assumes an increase in excitability of the thermal sweat centre in the hypothalamic region by fall-out of the tonic inhibitory action from the cerebral cortex during sleep. The findings on the sodium concentration of spontaneous sweat need further supplementation and will be the subject of further study.

The intrinsic abnormality of the sweat glands in cystic fibrosis might, as such, be responsible for this observation. On the other hand, an increased excitability of the hypothalamic sweating centre in cystic fibrosis cannot be ruled out at present. The purpose of this paper is to call attention to the abnormality in rate of secretion under these conditions. Further clarification of the many factors involved in such spontaneous nocturnal sweating is needed.

Summary

The pattern of spontaneous sweating over subsequent 24-hour periods was studied in three patients with cystic fibrosis and three control children. A marked difference in spontaneous night sweating rates was documented in 10 patients with cystic fibrosis and 10 control children. This finding may represent a non-specific abnormality in cystic fibrosis, but clearly shows another deviation of sweat gland function, possibly related to the specific pathophysiological mechanism responsible for the elevation of electrolytes in the sweat of patients with cystic fibrosis.

References

Amatruda, T. T., Jr. and Welt, L. G. (1953). Secretion of electrolytes in thermal sweat. *J. appl. Physiol.*, **5**, 759.

Cecil, R. L. and Loeb, R. F. (1959). *A Textbook of Medicine.* Saunders, Philadelphia and London.

di Sant'Agnese, P. A., Darling, R. C., and Perera, G. A. (1953). Sweat electrolyte disturbances associated with childhood pancreatic disease *Amer. J. Med.*, **15**, 777.

——, ——, —— and Shea, E. (1953). Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas. *Pediatrics*, **12**, 549.

Gochberg, S. H. and Cooke, R. E. (1956). Physiology of the sweat gland in cystic fibrosis of the pancreas. *Ibid.*, **18**, 701.

Harrison, T. R., Adams, R. D., Bennett, I. L., Jr., Resnik, W. H., Thorn, G. W. and Wintrobe, M. M. (1958). *Principles of Internal Medicine.* McGraw-Hill, New York, Toronto and London.

Kuno, Y. (1956). *Human Perspiration.* (American lecture series No. 285.) Thomas, Springfield, Illinois.

Schwartz, I. L., Thaysen, J. H. and Dole, V. P. (1953). Urea excretion in human sweat as a tracer for movement of water within the secreting gland. *J. exp. Med.*, **97**, 429.

Shwachman, H., Leubner, H. and Catzel, P. (1955). 'Mucoviscidosis'. In *Advances in Pediatrics*, ed. S. Z. Levine, vol. 7, p. 249. The Year Book Publishers, Chicago.

Sibinga, M. S. and Barbero, G. J. (1961). Studies in the physiology of sweating in cystic fibrosis. I. Experimental sweat gland fatigue. *Pediatrics.* **27**, 912.

Vink, C. L. J. (1957). The sweat test in cystic fibrosis of the pancreas. *Amer. J. Dis. Child.*, **94**, 40.

HYPOPHOSPHATASIA: A GENETIC STUDY

BY

J. C. RATHBUN, J. W. MACDONALD, H. M. C. ROBINSON and J. M. WANKLIN

From the Departments of Paediatrics, and Psychiatry and Preventive Medicine, University of Western Ontario, and the Paediatric Research Laboratory, War Memorial Children's Hospital, London, Canada

(RECEIVED FOR PUBLICATION MARCH 17, 1961)

Since hypophosphatasia was first described (Rathbun, 1948), other cases which have been recognized have raised the possibility that this defect of alkaline phosphatase is an inherited inborn error of metabolism. Schneider and Corcoran (1950) first suggested that this was an inherited disorder when two cases were found in one family, and this was corroborated by Sobel, Clark, Fox and Robinow (1953). McCance, Fairweather, Barrett and Morrison (1956) demonstrated reduced levels of serum alkaline phosphatase in three generations of one family, suggesting that this was a recessively inherited disorder in which the heterozygous state could be demonstrated by measuring the serum alkaline phosphatase or the phosphoethanolamine in the urine of carriers of the trait. Fraser (1957) then reviewed the literature and pointed out that 26% of reported siblings were affected: the expected incidence of a recessive characteristic. Kretchmer, Stone and Bauer (1958) tried unsuccessfully to identify heterozygous carriers by studies of alkaline phosphatase in leucocytes. Most recently, Harris and Robson (1959) have reported a study of 381 relatives of known cases by urinary chromatograms for phosphoethanolamine, demonstrating a manifestation rate of 0·58 with this method. Because of the importance in genetic counselling, it was felt worthwhile to study the family of two cases which have been under observation since 1954 and reported, in part, by Rathbun (1959).

The aim of the study was to determine, if possible, the definitive level of serum alkaline phosphatase indicative of the carrier state and the incidence of the carrier state in 30 relatives in three generations.

Material and Method

Serum alkaline phosphatase was measured using a modification of the method of Taussky and Shorr (1953).

Reagents. The following reagents were used:

Alkaline Phosphatase Substrate. 2·5 g. sodium glycerophosphate (beta); 2·12 g. sodium diethylbarbiturate.

Dissolve and dilute to 500 ml. with distilled water. The solution is kept under toluene in the refrigerator. The *p*H, when mixed with one-tenth its volume of serum, should be 8·5.

35% *Trichloracetic Acid Solution* (*wt./wt.*). 35 g. TCA dissolved in 65 g. water.

Ammonium Molybdate Solution—10%. 50 g. of $(NH_4)_6Mo_7O_{24}.4H_2O$ are weighed into a litre beaker and about 400 ml. of 10N sulphuric acid are added with constant stirring to prevent caking. When completely dissolved, the solution is transferred to a 500 ml. volumetric flask and washed in quantitatively with 10N sulphuric acid to 500 ml. mark.

Sulphuric Acid 10*N*. 278 ml. of concentrated sulphuric acid are slowly added to about 700 ml. distilled water. After cooling, the solution is further diluted to 1,000 ml.

Ferrous Sulphate—Ammonium Molybdate Reagent. This must be made up freshly before use. 10 ml. of ammonium molybdate stock solution are transferred to a 100 ml. amber volumetric flask and diluted to about 70 ml.; 5 g. $FeSO_4.7H_2O$ are added and the solution is made up to volume and shaken until the crystals are dissolved.

Phosphate Stock—100 *mg.*/100 *ml.* 450 mg. KH_2PO_4 are heated in an oven at 80 degrees centigrade for 24 hours and cooled in a desiccator over night. Of this, 438 mg. KH_2PO_4 are dissolved and diluted to 100 ml. with distilled water and kept under toluene.

Phosphate Working Reagent. 2 ml. stock solution is diluted to 100 ml. with distilled water. This keeps for one week.

Method. Start with enough tubes (12 × 100 mm.) to take a water blank, two phosphorus standards and four tubes for each serum sample (two of these will be for incubated and two for non-incubated serum). Into each tube measure 1 ml. substrate solution and place all the tubes in 37° C. water bath for five minutes. To two of the tubes add 0·1 ml. serum, mix well, close with 'Parafilm' and return to the 37° C. water bath for exactly 60 minutes. After one hour, the tubes are placed in an ice bath for five minutes, during which time 0·5 ml. of 35% TCA solution is added to each tube; mix well. The tubes are removed and placed at room temperature for five minutes, during which time 0·1 ml. water, standard phosphate working solution and serum are added, respectively, to the remaining tubes; mix well.

All tubes are centrifuged for five minutes at 2,000 r.p.m. in groups starting with incubated serum. Supernatant (1 ml.) from each tube is placed in 12 × 75 mm. cuvettes and 1 ml. ferrous sulphate ammonium molybdate reagent is added to each cuvette. Mix well. After five minutes, the cuvettes are read in the Coleman spectrophotometer at 680 mμ.

Blood Collection. Members of the family group and a control subject with a known normal range of serum alkaline phosphatase were tested simultaneously to eliminate false values due to technique or reagent variation. Tests were performed in groups of three family members and one control subject. Blood samples were drawn from the four subjects within a total period of about 15 minutes and the determinations were performed on the serum as soon as it was separated by centrifugation. Because serum values change if the determination is not performed at once, family members were assembled in two hospitals near their homes. For these family members in out-of-town hospitals, all the tests were performed using the same technique, equipment and reagents as in the War Memorial Children's Hospital Research Laboratory.

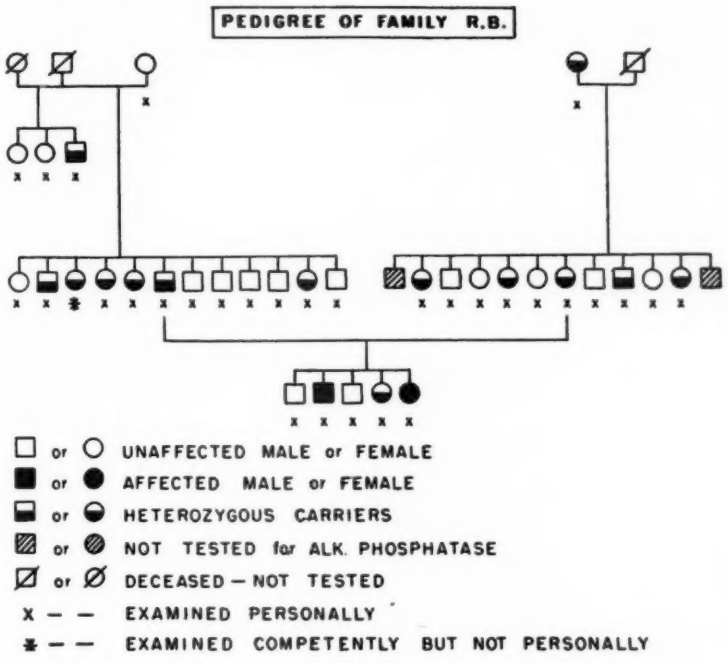

PEDIGREE OF FAMILY R.B.
or UNAFFECTED MALE or FEMALE
or AFFECTED MALE or FEMALE
or HETEROZYGOUS CARRIERS
or NOT TESTED for ALK. PHOSPHATASE
or DECEASED — NOT TESTED
EXAMINED PERSONALLY
EXAMINED COMPETENTLY BUT NOT PERSONALLY

FIG. 1.

The supernatant fluid obtained after deproteinization was kept refrigerated overnight. The colour was then developed with ferrous sulphate ammonium molybdate reagent. Separate experiments have shown that the phosphorus values are not affected by the overnight storage. All members of the control group were apparently healthy nurses, medical students, doctors and other hospital employees. A scatter diagram revealed no trend of variation in values with age among the adult population sampled.

Results

Stern (1947) has shown that females have lower values than males and the results were therefore separated into sex groups.

Table 1 shows the results obtained in the male relatives of the known cases, while Table 2 shows the results of the female relatives.

Table 3 gives the results of the examination of the siblings and Fig. 1 illustrates the family pedigree where heterozygous carriers were considered to be all persons with levels of serum alkaline phosphatase below 2·0 Bodanski units, regardless of sex.

TABLE 1
MALE RELATIVES OF PARENTS

Maternal		Paternal	
Name	Alkaline Phosphatase (Bodansky units)	Name	Alkaline Phosphatase (Bodansky units)
J.B.	1·8	P.B.	1·4
C.B.	3·1	Ra.B.	1·6
V.B.	3·4	Ph.B.	1·6
		R.B.	1·9
		J.B.	2·2
		Gd.B.	2·7
		G.B.	3·5
		Re.B.	3·5

Normal mean 2·7 ± 0·58

TABLE 2
FEMALE RELATIVES OF PARENTS

Maternal		Paternal	
Name	Alkaline Phosphatase (Bodansky units)	Name	Alkaline Phosphatase (Bodansky units)
L.B.	1·1	C.R.	1·3
L.B.	1·4	B.B.	1·5
L.C.	1·7	D.P.	1·6
B.	1·7	J.B.	1·6
N.A.	1·7	A.H.	1·8
R.B.	2·0	B.M.	2·4
D.M.	2·5	B.	2·4
B.T.	2·6		

Normal mean 2·4 ± 0·7

TABLE 3
SIBLINGS OF CASES

Siblings		
Name	Sex	Alkaline Phosphatase (Bodansky units)
R.	M	6·1
R.	F	3·5
J.	M	5·0

TABLE 4

MEAN SERUM ALKALINE PHOSPHATASE LEVELS (BODANSKI UNITS): FAMILY MEMBERS *vs.* CONTROLS BY SEX

	Family Members			Controls		
	No.	Mean	S.D.	No.	Mean	S.D.
Males ..	11	2·4	±0·8	18	2·6	±0·7
Females ..	15	1·8	±0·4	24	2·4	±0·7
Total ..	26	2·1	—	42	2·5	—

TABLE 5

ANALYSIS OF VARIANCE ON DATA IN TABLE 4

Source of Variation	Degrees of Freedom	Sums of Squares	Mean Square	F	P
Experimental group	1	2·96	2·96	6·58	<0·05
Sex	1	1·92	1·92	4·27	<0·05
Groups *vs.* sex interaction	1	0·99	0·99	2·20	>0·05
Residual	64	29·11	0·45	—	—
Total	67	34·98	—	—	—

Statistical Analysis

The control group consisted of 18 males and 24 females, and therefore equated with the family group in terms of sex ratio (Table 4).

Statistical significance ($p < 0{\cdot}05$) could be attached to a reduction of 0·4 units in the overall mean value for the family group, as well as to a tendency for females generally to have lower values than males. However, a further tendency for values in the family group to be reduced more for females than for males failed to attain statistical significance.

Discussion

When these figures of the family group are compared with normal controls, not separated for sex, using analysis of variance (Snedecor, 1946) the difference is significant (Table 5). Hence it appears feasible to separate the carriers by this method. As the father (R.B.) had a level of 1·9 B.U. and the mother (B) had a level of 1·7 B.U., it is reasonable to state that the heterozygous carrier level in the male and female exists at levels at, and below, 1 S.D. of the normal mean. These figures suggest that a level below 2 Bodanski units of serum alkaline phosphatase is indicative of the heterozygous carrier state for at this level 50% of the examined aunts, uncles and parents are shown to be carriers; this is the expected incidence. This level will include, however, about 15% of normal persons owing to the overlapping of the normals with heterozygous carriers. Further careful studies may allow a more precise evaluation.

It has been our experience that the assay of serum alkaline phosphatase is plagued with many difficulties, and if the technique is not well controlled the results may be valueless. Unfortunately, in the literature, there are a wide variety of methods of determining the serum alkaline phosphatase. The results of one observer cannot be compared directly with those of another because of different methods used, even though these results are qualitatively similar. This has produced chaos in this field.

The evidence put forward by Harris and Robson (1959), together with the studies presented here, confirms the fact that hypophosphatasia is an inherited recessive disease in which the carrier state can be detected in most cases. The importance of this in genetic counselling needs no emphasis.

Conclusions

Hypophosphatasia is inherited as a recessive characteristic.

The carrier state is represented by adult persons with serum levels below 2 Bodanski units.

The normal level for males is $2{\cdot}7 \pm 0{\cdot}58$ Bodanski units and for females is $2{\cdot}4 \pm 0{\cdot}7$ Bodanski units.

A plea for uniformity in chemical determinations is made.

The cases studied were referred by Dr. William L. Wilford, Wallaceburg, Ontario. As a result of his interest and the interested co-operation of the B. family, this study became possible. Our thanks also go to the Sydenham District Hospital, Wallaceburg, and to the Hotel Dieu Hospital, Windsor, Ontario, for the use of their Laboratories.

Our appreciation is extended to Dr. E. Harpur of Montreal Children's Hospital for the determination on one of the relatives.

REFERENCES

Fraser, D. (1957). Hypophosphatasia. *Amer. J. Med.*, **22**, 730.

Harris, H. and Robson, E. B. (1959). A genetical study of ethanolamine phosphate excretion in hypophosphatasia. *Ann. hum. Genet.*, **23**, 421.

Kretchmer, N., Stone, M. and Bauer, C. (1958). Hereditary enzymatic effects as illustrated by hypophosphatasia. *Ann. N.Y. Acad. Sci.*, **75**, 279.

McCance, R. A., Fairweather, D. V. I., Barrett, A. M. and Morrison, A. B. (1956). Genetic, clinical, biochemical and pathological features of hypophosphatasia. Based on the study of a family. *Quart. J. Med.*, **25**, 523.

Rathbun, J. C. (1948). Hypophosphatasia; a new developmental anomaly. *Amer. J. Dis. Child.*, **75**, 822.

—— (1959). Hypophosphatasia. *Helv. paediat. Acta*, **14**, 548.

Schneider, R. W. and Corcoran, A. C. (1950). Familial nephrogenic osteopathy due to excessive tubular reabsorption of inorganic phosphate: a new syndrome and a novel mode of relief. *J. Lab. clin. Med.*, **36**, 985.

Snedecor, G. W. (1946). *Statistical Methods*, 4th ed. The Iowa State College Press, Ames, Iowa.

Sobel, E. H., Clark, L. C., Jr., Fox, R. P. and Robinow, M. (1953). Rickets, deficiency of 'alkaline' phosphatase activity and premature loss of teeth in childhood. *Pediatrics*, **11**, 309.

Stern, M. I. (1947). Levels of serum alkaline phosphatase among infants (2-27 months) in the British Zone of Germany. *Brit. J. Nutr.*, **1**, 182.

Taussky, H. H. and Shorr, E. (1953). A microcolorimetric method for the determination of inorganic phosphorus. *J. biol. Chem.*, **202**, 675.

HYPERNATRAEMIC DEHYDRATION IN INFANTILE GASTRO-ENTERITIS

BY

DUNCAN MACAULAY and MARGARET I. BLACKHALL
From the Duchess of York Hospital for Babies, Manchester

(RECEIVED FOR PUBLICATION DECEMBER 19, 1960)

Although it is possible to find occasional reports written before the last war of the occurrence of hyperelectrolytaemia in sick infants and children (for early references see Rapoport, 1947) the recognition of the condition as a fairly common one and the elucidation of the clinical features date from 1947 when Rapoport gave an account of 14 patients with hyperosmolarity of the plasma. Of the 14 patients, 10 were suffering from diarrhoea. Five of these were noted to have symptoms of central nervous system disturbance, from marked lethargy to convulsions. The first indication of the possible frequency of this state came in a report by Tarail, Bass and Runco (1953) who found that, of 191 infants with diarrhoea, 21 or 11% had serum sodium levels of 150 mEq/litre or higher. In 1955 Finberg and Harrison gave an account of seven years' experience of infantile diarrhoea involving 274 patients. They reported an incidence of hypernatraemia (serum sodium level over 150 mEq/l.) of 25% and pointed out the great frequency of 'manifestations referable to the nervous system', nearly two-thirds of the hypernatraemic cases showing such signs. They reported, for the first time, the occurrence of raised protein concentrations in the cerebrospinal fluid, and drew attention to the fact that nearly half the cases did not show the customary signs of dehydration. They indicated the danger that rapid rehydration with dilute fluids might give rise to symptoms similar to those seen in water intoxication, especially to convulsions, and they suggested that hypernatraemia could be a cause of permanent brain damage. This paper seemed to define a distinct clinical entity of considerable significance. It was followed by one by Weil and Wallace in 1956 which emphasized the points made by Finberg and Harrison, especially the neurological disturbances. Several other papers from America have reported similar findings and opinion in that country is probably represented by the account of 'Hypertonic dehydration' given by Cooke (1959). According to this writer hypertonic dehydration occurs in approximately 20% of cases of diarrhoea in infancy; 'of particular importance are the cerebral changes which result from severe hyperosmolarity'; the development of oedema during treatment is referred to as 'characteristic'.

From consideration of the available reports the 'clinical picture' of hypertonic dehydration emerges as follows: the patients are predominantly infants in the first year of life; as the result of fluid loss in the stools and by vomiting there is often loss of 10-15% of the body weight without the classical signs of such a severe degree of dehydration, e.g. the skin turgor may be deceptively normal; symptoms and signs of cerebral damage are common and include disturbances of consciousness ranging from lethargy to coma; hyperirritability to stimuli in spite of extreme lethargy; increased muscle tone amounting in many cases to generalized rigidity with very brisk tendon reflexes; convulsions, especially during rehydration; raised concentration of protein in the cerebrospinal fluid and rather exceptionally, the development of sub-dural effusions. Oedema is liable to appear during the administration of rehydrating fluids, sometimes before full rehydration has been effected. It has been suggested (Franz and Segar, 1959) that this state is becoming commoner and also (Finberg, 1958) that it may be due in many instances to the unwise administration of fluids with 'high-solute' content.

We wish to describe the two cases which first drew our attention to this condition and then to give an account of an analysis of the records of 100 infants with diarrhoea admitted to the Duchess of York Hospital for Babies on whom serum-electrolyte estimations were performed.

Case Reports

Case 1. A baby girl, 3 months of age, was admitted to hospital with a history of diarrhoea and vomiting for five days. She had been perfectly well before then. On the day of admission, after a vomit, she became pale,

limp and staring; her breathing was rapid and grunting and she was sent to hospital as '? pneumonia'. On admission she was an ill infant, pale and listless, with a temperature of 102° F. The skin turgor was considered to be good and the fontanelle was not depressed, but the tongue was dry. The reflexes were brisk. There were a few moist sounds in the right lung. Otherwise examination revealed no abnormalities. Serum electrolyte estimation showed well-marked hypernatraemia and mild acidosis (serum Na 168, K 5·7, CO_2 16·2, Cl 144 mEq/l.). About 24 hours after admission the child was found convulsing. Lumbar puncture was performed. The fluid was slightly blood-stained and had a protein content of 80 mg./100 ml. and a high chloride concentration (137 mEq/l.). Serum electrolytes were rechecked at this time and showed persistence of the hypernatraemia (serum Na 159 mEq/l.). In view of this, the fluid intake was increased. The following day the baby had another convulsion and she was so drowsy throughout the day that she had to be fed by tube. On the sixth day the fontanelle was noted to be quite full and subdural taps were performed. From the left side 6 ml. of blood-stained fluid were obtained and from the right side about 2 ml. of turbid fluid. After this there was persistent oozing of fluid from the puncture on the right side for about 24 hours. Thereafter progress was uneventful and the infant was discharged after 17 days in hospital.

Two days after discharge diarrhoea and vomiting recurred and persisted for six days and she was readmitted to hospital. She was again quite a seriously ill child; the temperature was 103·4° F. and she was listless but very jumpy. On this occasion, however, there were marked signs of dehydration; lax skin, dry mouth and sunken fontanelle; after blood for electrolyte estimation was obtained, an intravenous infusion was started. The serum chemistry again showed pronounced hypernatraemia with severe acidosis (serum Na 162, K 6·6, CO_2 8·5, Cl 128 mEq/l.). Twelve hours after admission the child was convulsing again and anticonvulsants were administered. On the second day the serum sodium was normal and it remained normal on two subsequent examinations. Progress was rapid and she was discharged after 11 days. Just before discharge, when she was clinically and chemically normal, renal function tests were carried out. Urea clearance was 90% of normal and the output of sodium and chloride in the urine was normal for the estimated intake.

Six weeks after discharge she was seen as an outpatient and apart from mild constipation she seemed well in every way.

Case 2. A 10-week-old baby boy was admitted with a 24-hour history of diarrhoea. He had not vomited but was reluctant to feed and on the morning of the day of admission he had felt cold. Later that day he seemed to have difficulty with breathing and his colour became poor. On admission he was a very ill baby. The temperature was 104° F.; breathing was rapid and irregular and there was a tinge of cyanosis; he was extremely limp and listless. Hydration was considered to be good; the skin turgor was not appreciably reduced and the fontanelle was not depressed. There were no localizing signs on examination and the diagnosis was obscure. Encephalitis was thought to be a possibility and lumbar puncture was performed. The fluid was slightly turbid from the presence of red blood cells; no organisms were seen on smears and cultures remained sterile. The protein content was 40 mg./100 ml. and the chloride concentration very high (162 mEq/l.). On the morning after admission the infant was still extremely ill and had a high-pitched cry. Fever persisted and a macular rash was present on the trunk. Serum electrolyte examination revealed gross hypernatraemia (serum Na 180, K 6·2, CO_2 16·7, Cl 135 mEq/l.). There was a pronounced leucocytosis in the peripheral blood and the urine contained albumen. All other investigations gave normal results. Diarrhoeal stools were passed for a week. On the third day oedema of the legs was noticed; this persisted for nearly a week. In the afternoon of that day he began to convulse. Just before the onset of the convulsion the limbs were stiff and after it he was lethargic and had to be fed by tube. At this stage the blood still showed hypernatraemia (serum Na 153 mEq/l.). On the fourth day sub-dural taps were done. About 2 ml. of blood-stained fluid were obtained from each side. The profound lethargy continued for another two days and then quite quickly the baby began to improve and he was discharged on the fourteenth day apparently well. Two months after discharge he seemed a perfectly normal infant.

These two cases fulfilled many of the criteria laid down by the American workers for this syndrome; they had lost 10% and 11% of their body weight (as judged by the weight-gain on rehydration) which puts them in the category of moderately severe dehydration, but, except in the second admission of Case 1, they were not considered to be in need of immediate intravenous fluids. In other words the customary signs of such a degree of dehydration were absent. They showed several of the nervous disturbances mentioned previously, notably profound lethargy, and convulsions during rehydration. Small sub-dural effusions occurred in both patients. In one the C.S.F. protein was high and in the other at the top limit of the normal range for an infant of this age. One of them became oedematous during treatment.

Analysis of Case Records

Micro methods for serum electrolyte estimation became available at the Duchess of York Hospital for Babies towards the end of 1957. The case notes of all patients who had this estimation carried out from October 1, 1957, till June 30, 1960, were examined. In this period of two years and nine months, 98 patients with diarrhoea had serum electrolyte estimations performed. For ease of calculation of percentages we have made the figure up to 100 by including the first two cases examined in July 1960. The series thus consists of 100 consecutive patients admitted to the hospital suffering from diarrhoea on whom figures for serum electrolytes were obtained.

During the period covered by this survey 439 patients were admitted with diarrhoea. Thus, rather less than

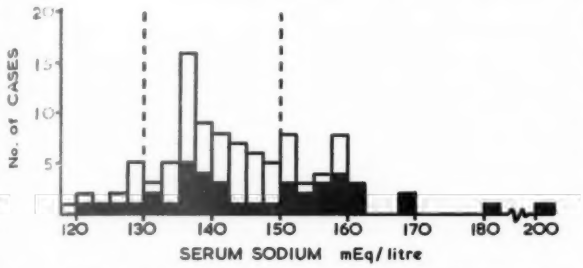


FIG. 1.—Distribution of serum sodium levels at intervals of 2·5 mEq/l. Vertical dotted lines demarcate hypo-, normo- and hypernatraemia. Cases showing nervous disturbances are indicated in black.

25% of them were examined in this way. In general it was the more seriously ill patients who had this examination performed. Because of this selection care must be exercised in making general statements about infants with diarrhoea.

Criteria and Results

The 'normal serum sodium concentration ranges from 135 to 145 mEq per litre' (Cooke and Ottenheimer, 1960). We have adopted the standard of Harrison and Finberg (1959) that any value for serum sodium of 150 mEq/l. or above constitutes hypernatraemia. The range of values for serum sodium in this series was from 118 to 200 mEq/l. The distribution of the measurements is shown in the Figure. It can be seen that 150 mEq/l. is an obvious level at which to separate the cases, the step-wise decrease in numbers being replaced at that point by a sharp increase.

In Table 1 are listed the reports available to us with the percentages of cases in the various groups. The incidence of hyponatraemia (serum sodium of 130 mEq/l. or less) is fairly constant in all the series in which it is listed. There is marked variation, however, in the incidence of hypernatraemia which cannot be satisfactorily explained on the information available. However, in the nine series in which actual figures are given, of a total of 976 infants, 206 or 21% were hypernatraemic. Our series contains more hypernatraemic cases than the average, but considerably fewer than in two of the reports. We have thus established that hypernatraemic dehydration is as common here as in other areas.

Mortality. Eight of the 100 patients died. In two cases death might be attributed directly to the diarrhoea. One was a mongol who responded poorly to treatment; the second baby died a week after admission and at autopsy was found to have extensive ulcerative colitis. Two other children died several weeks after the initial attack of diarrhoea and at autopsy showed only bronchopneumonia; one of these was also a mongol. The remaining four patients died at intervals of from three to 30 days after the serum electrolyte measurement and all four showed gross cerebral changes at autopsy. The pathological conditions were described as follows: multiple cerebral haemorrhages; multiple areas of cerebral necrosis; cerebral infarction; and multiple areas of cerebral necrosis with calcification. It is a striking fact that three of these four 'cerebral' deaths occurred among the 30 patients with hypernatraemia—indeed they were the only deaths in this group—while only one occurred in the remaining 70 patients. This bears out what must, we think, be accepted as an established fact, that there is an association between hypernatraemia and brain injury.

Contrary to the experience of others, hypernatraemia did not in this series carry a significantly higher mortality than normo- or hyponatraemia, the overall mortality in the former being 10% and in the latter 7%.

Neurological Disturbances. Clinical evidence of disturbances of the nervous system is most con-

TABLE 1
INCIDENCE OF HYPO- AND HYPERNATRAEMIA IN PREVIOUS REPORTS

Authors	Year	Country	Hyponatraemia (%)	Normonatraemia (%)	Hypernatraemia (%)	No. of Cases
Tarail *et al.*	1953	U.S.A.			11	191
Finberg and Harrison	1955	U.S.A.			25	274
Weil and Wallace	1956	U.S.A.	10	70	20	77
Skinner and Moll	1956	U.S.A.			23	61
Kerpel-Fronius and Vönöcsky	1957	Hungary	9	76	15	113
Colle *et al.* (*a*)	1958	U.S.A.			16–25	
Colle *et al.* (*b*)	1958	U.S.A.			71	24
Bowie *et al.*	1958	S. Africa	22	44	34	32
Frank and Segar	1959	U.S.A.			4–21	
Darrow and Welsh	1960	U.S.A.	14	75	11	104
Mayalay and Blackhall (this paper)	1961	U.K.	11	59	30	100
Averages			12	67	21	
Total						976

vincingly documented by the occurrence of convulsions and by the frequency with which lumbar puncture was performed. It is reasonable to suppose that a child subjected to lumbar puncture must have had some symptom or sign suggestive of C.N.S. disorder. Convulsions were recorded in 10 of the hypernatraemic group, in nine of them during rehydration, and in seven of the remaining cases, five of these occurring during treatment. Statistically this difference is significant at the 2% level and almost reaches the 1% level. The difference between the two groups in the frequency with which lumbar puncture was performed (14 or 47% of the hypernatraemic patients, 17 or 24% of the remainder) is just significant at the 5% level. A less reliable, because more subjective, criterion of nervous disorder is recording disturbances of consciousness. These ranged from marked lethargy to deep coma. Since the existence of the syndrome of hypernatraemic dehydration was, we are confident, unsuspected by the observers making the notes any bias in recording this symptom should affect all cases equally. In this case the difference between the two groups is highly significant. Of the hypernatraemic patients 14 (47%) and of the remainder 12 (17%) showed some depression of consciousness ($p < 0{\cdot}01$).

The protein concentration in the cerebrospinal fluid was estimated in 14 samples from hypernatraemic patients and in 15 from other cases. The values ranged very widely in both groups—from 20 to 200 mg./100 ml. in the former, from 20 to 500 mg./100 ml. in the latter. The average value in the hypernatraemic patients was 70 mg./100 ml., and in the others 80 mg./100 ml. This latter figure is a little misleading as there were two very high values in this group. If 40 mg./100 ml. is taken as the upper limit of normal, there were nine high values in the 14 hypernatraemic samples and six in the 15 from the other patients. This difference, though suggestive, is not significant ($p > 0{\cdot}3$). We have, in other words, failed to confirm that hypernatraemia is regularly associated with raised protein levels in the cerebrospinal fluid.

The incidence of hyperirritability and increased muscle tone could not be determined with any accuracy from the records available since they were infrequently noted in any group.

The follow-up period was, for many patients, too short to permit any evaluation of ultimate neurological status.

There is, in the present series as in those previously reported, definite evidence of an association between hypernatraemia and nervous disturbances. However, it is not a consistent relationship. In the 30 hypernatraemic patients no record of any neurological upset was found in 11 cases. Contrariwise, 22 of the 70 non-hypernatraemic patients had one or more of the symptoms of nervous disorder mentioned in the introductory paragraphs (see also the distribution of cases with nervous disturbances in the Figure). In terms of the numbers at risk there were twice as many patients with neurological disturbances in the hypernatraemic group as in the remainder. A small number of the latter would undoubtedly have been diagnosed on clinical grounds as hypernatraemic, and a considerable number of the former would have been misdiagnosed on the evidence of clinical observation. Since becoming interested in the subject we have made both these mistakes and conclude that the clinical diagnosis of hypernatraemia is unreliable.

TABLE 2
SIGNS OF DEHYDRATION IN CASES WITH WEIGHT LOSS OF 10% OR MORE

Clinical Assessment of Degree of Dehydration	Hypernatraemic Cases	Other Cases
0	3	1
+	5	6
Total 0 and +	8	7
++	5	11
+++	1	3
Total ++ and +++	6	14

$\chi^2 = 1{\cdot}09 \quad p = 0{\cdot}3$

Signs of Dehydration. As noted in the introduction, the extent of fluid loss in hypernatraemic dehydration is said to be often underestimated because of the lack of the usual signs of dehydration. We have tried to assess this factor in the following way. In some cases, e.g. hospital-acquired infections, the weight before the onset of the diarrhoea was known. In the others the weight charts were used to estimate the gain in weight due to rehydration. From these data the amount of weight lost as the result of the diarrhoea was estimated and expressed as a percentage of the normal weight. Of the 85 patients whose records were complete enough to permit these calculations 35 were estimated to have lost 10% or more of their body weight, i.e. were moderately severely or very severely dehydrated. The clinical assessment of the degree of dehydration in these cases is shown in Table 2. We are not perturbed by the lack of precision in the terms used in recording the apparent degree of dehydration, nor by the fact that nearly half the cases (15 of the 35) were wrongly assessed. The point at issue is whether this mistake is more common when the patient is hypernatraemic. In fact

the distribution of the cases in this Table does not differ from chance expectancy. Our subsequent experience confirms this finding and we have found it impossible to predict the serum sodium level from the apparent severity of clinical dehydration.

Oedema. Oedema was noted to have occurred in six of the 30 hypernatraemic cases during treatment and in only two of the 70 others. While this is an interesting observation, and indeed a 'significant' one in the statistical sense (the probability of it being a chance occurrence is very nearly one in 100), it hardly bears out the contention that the development of oedema is characteristic of the hypernatraemic state. Mild degrees of oedema may have escaped notice and close observation might yield higher figures. We find it hard to believe, however, that appreciable oedema is at all common in hypernatraemic infants.

Aetiological Factors

We have reviewed our cases to try to determine what factors might have resulted in 30 of them becoming hypernatraemic. In order to permit statistical evaluation we have given numerical values to the data wherever possible. The notes are not equally informative in all cases and we show the numbers of cases in which the data were considered satisfactory either in the Tables or in brackets after each sub-heading.

No difference between the hypernatraemic patients and the others was found in respect of the following items and we shall not give detailed figures: sex, age, premature birth, previous history of nervous or renal disease, seasonal incidence (the absence of any climatic influence is shown by the numbers with hypernatraemia occurring in successive six-monthly periods, *viz.* five, five, four, five, six), frequency of vomiting, character of stools (whether merely 'loose' or described as 'watery'), or number of stools per day. The amount of sodium in the diet before the electrolyte estimation was not a factor in the development of hypernatraemia, but in view of the importance attached to this by some American writers, we shall consider it in some detail.

Sodium Intake. The object of this analysis was to see if, as has been claimed (Finberg, 1958), excessive administration of salt-containing fluids was responsible for a significant number of patients becoming hypernatraemic. This is of obvious importance, since it might lead to recommendations which could result in reducing the number of infants with this complication of diarrhoea.

TABLE 3
ESTIMATED SODIUM INTAKE

Sodium Intake (mEq/kg./day)	Group		
	Hypo-natraemia	Normo-natraemia	Hyper-natraemia
< 5	5	23	16
5–10	5	17	9
>10		3	2
Totals	10	43	27

Where the information available made it feasible, we have attempted to assess the sodium intake of the patients in the 48 hours before the electrolyte estimation was done. Very few of the patients were given supplementary salt-containing fluids before admission. This represents a marked difference from experience in America (Colle, Ayoub and Raile, 1958; Franz and Segar, 1959; Harrison and Finberg, 1959) where commercial electrolyte solutions are extensively used in the home treatment of diarrhoea. These estimates cannot, obviously, be very precise, but in 80 of the 100 cases there were sufficient data to justify analysis. We have calculated the amount of sodium in the feeds *offered* to the infants, ignoring vomiting and anorexia as sources of error. This means that our estimates are of the greatest amounts of sodium likely to have been ingested. In many cases, because of vomiting and anorexia, the actual intakes were much less than those calculated. The sodium content of various feeds was directly measured by having random feeds, made up in the hospital milk-room, analysed in the laboratory. The figures are given in terms of mEq sodium/kg. hydrated body weight/day. This makes possible comparison of babies of different weights and it also indicates the importance of the actual load of sodium given. There is some evidence that 'the ceiling for renal excretion of sodium may be in the range of 5 to 10 mEq per kilogram of body weight per day' (Skinner and Moll, 1956). Darrow and Welsh (1960) report that quantities equivalent to 7·5 mEq/kg./day are well tolerated by infants not suffering from dehydration. It may be assumed that intakes of up to 5 mEq/kg./day are normal (e.g. an infant fed on a half-cream dried milk at the rate of 2½ oz./lb./day will ingest approximately 4 mEq/kg./day). Intakes of over 10 mEq/kg./day are almost certainly excessive. The intermediate amounts, 5 to 10 mEq/kg./day, would probably be tolerated without difficulty by a healthy infant, but might be excessive for an ill one.

The results of our analysis are given in Table 3. Only five infants received amounts of sodium in the frankly excessive range (four of them had been

rather enthusiastically rehydrated with intravenous fluids before the electrolytes were measured) and of these only two showed hypernatraemia. More than half the hypernatraemic group had been offered, and had not necessarily ingested, quite normal amounts of sodium. In the intermediate group the distribution of cases is almost exactly the same as in the series as a whole, *viz.* 29% hypernatraemic. It seems legitimate to conclude that very few of our patients had been overloaded with sodium and that dietary sodium played an insignificant part in determining the serum sodium levels.

The respects in which the hypernatraemic cases differed from the others were: severity of anorexia, duration of diarrhoea, temperature and respiratory rate.

Anorexia. The severity of anorexia has been graded as 0 (none), + (mild, 'reluctant to feed') and ++ (severe, 'refused all feeds'). The results of the analysis are shown in Table 4. The difference between the groups is highly significant—60% of the hypernatraemic group having had severe anorexia compared to 24% of the others.

TABLE 4
SEVERITY OF ANOREXIA IN HYPERNATRAEMIC AND OTHER PATIENTS

Severity of Anorexia	Group		Totals
	Hypernatraemic	Others	
0 or +	10	45	55
++	16	14	30
Totals ..	26	59	85

$\chi^2=9\cdot7$ $p<0\cdot01$

Duration of Diarrhoea (94 cases). The mean duration of diarrhoea before admission, or before blood examination in those developing diarrhoea in hospital, was 3·4 days for the hypernatraemic group and 5·7 days for the others. This is a significant difference ($t = 2\cdot16$; $0\cdot05 > p > 0\cdot02$). None of the patients in the first group had been ill for longer than seven days, and several for only a few hours; whereas in the latter groups 18 out of 68 had histories longer than a week.

Temperature (100 cases). The highest temperature recorded on the day of admission (or on the day of electrolyte estimation, if these were different) had been taken as an index of the severity of fever. In most cases, but not in all, these were the highest temperatures recorded during the child's stay in hospital. The average temperatures, and the standard deviations, in the groups were: hypernatraemic cases 100·8° F. ± 2·6; remainder 98·6° F. ± 1·9. This difference of 2·2° F. between the means is nearly five times as great as its standard error and is thus highly significant. Nearly half the hypernatraemic cases had fever of 101° F. or more (14 out of 30), whereas only one in 10 of the remaining cases (seven out of 70) showed such a response.

Respiratory Rate. The respiratory rate at the time of recording the temperature used in the previous section has been tabulated in the same way. Unfortunately, owing to a change in the type of chart used in the wards during the period of this survey, these figures are available for only 46 patients. There is no reason to believe that this has resulted in any bias in the figures: the proportions in the various groups do not differ appreciably from those in the series as a whole: 16 of the 46 were hypernatraemic. In most cases, of course, the respiratory rate paralleled the temperature, but in a small number there was a disproportionate hyperpnoea. The average rates in the groups (with their standard deviations) were as follows: hypernatraemic cases 49/min. ± 13·8; others 34/min. ± 5·9. This is also a very highly significant difference ($t = 4\cdot67$; $p < 0\cdot001$). Of the hypernatraemic cases 75% (12 out of 16) had respiratory rates of 40/min. or above, while only one in 10 (three out of 30) of the others had so marked a tachypnoea.

Discussion

In this series of 100 infants with gastro-enteritis hyperosmolarity of the plasma, as measured by serum sodium levels, occurred in nearly one-third of the patients. In one-third of these there were no characteristic clinical features to differentiate them from other cases of infantile diarrhoea. In the other two-thirds nervous disorders of varying severity, from lethargy to extensive cerebral necrosis, were encountered. This incidence is similar to that reported by other writers (Finberg and Harrison, 1955). On the other hand about 30% of patients without hypernatraemia demonstrated neurological disturbances of the same type and severity. We have been unable to confirm that hypernatraemic dehydration is regularly associated with increased protein levels in the C.S.F. or that oedema is a frequent occurrence in this condition. We have not found the clinical assessment of the severity of dehydration a reliable index of the presence or absence of hypernatraemia.

The infants with hypernatraemia differed from the others in the following respects: incidence of

cerebral disturbances, short duration of diarrhoea, frequency of fever and tachypnoea and severity of anorexia.

This account agrees substantially with that given by Bowie, McKenzie and Hansen (1958) from which we quote: 'The clinical recognition of hyperosmolarity in infantile gastro-enteritis is difficult . . . It is our impression that those showing the hyperosmolar state had a short history of explosive diarrhoea and vomiting . . . Where gastro-enteritis is associated with hyperpyrexia, hyperventilation or severely curtailed fluid intake the possibility of hyperosmolarity developing is considerably enhanced.'

The pathogenesis of the condition does not seem to be particularly mysterious. It is known (Weil and Wallace, 1956) that diarrhoeal stools are hypotonic so that profuse diarrhoea will, in the absence of any compensating mechanism, lead to a greater deficit of water than of electrolyte, i.e. to a condition of hypertonicity. The two possible compensating mechanisms available are (1) an increase in the amount of water ingested to balance the losses and (2) differential excretion of electrolytes and water by the kidneys resulting in the secretion of a concentrated urine and maintenance of the tonicity of the body fluids. In infants neither of these mechanisms is as effective as in adults: (1) Infants are dependent on others for their fluid intake and the need for increased amounts of fluid may not be appreciated by the attendants. Even with an appreciation of these needs, severe anorexia may make it impossible to get enough fluid into the child. This was an important factor in our patients. (2) Under the stress of dehydration, and perhaps aggravated by losses of electrolytes, especially potassium, in the stools, renal function becomes impaired and the infantile kidneys become incapable of excreting a concentrated urine. The few studies reported on hypernatraemic infants (Weil and Wallace, 1956) confirm the existence of this type of dysfunction, manifested by the failure to excrete as concentrated a urine as would have been expected. This temporary renal failure is made worse by further losses of water from the skin and lungs through fever and hyperventilation. It may also contribute to further dehydration since the kidneys will require a greater volume of water for the excretion of solutes than if they are functioning normally.

In any event the development of hyperosmolarity is determined by disproportionate losses of water relative to sodium. This can occur without diarrhoea, and, in fact, the highest level of serum sodium encountered in any case in the two years and nine months of our survey was 235 mEq/l. (duplicate estimation) in an infant with congenital pyloric stenosis who was constipated but dehydrated and wasted from persistent vomiting.

With regard to treatment, recommendations have varied from elaborate schedules (Skinner and Moll, 1956) to statements that 'Patients with hypernatraemia received the usual fluid therapy used in other cases of diarrhoea' (Darrow and Welsh, 1960). In general it is agreed that repair solutions should be hypotonic and that the replacement of deficits should be spread over 48 hours. Our custom is to use 'fifth-normal saline in glucose water', i.e. a solution containing 0·18% NaCl and 4·3% glucose, and half-strength plasma, as repair solutions in all cases of diarrhoea requiring intravenous fluids. In the presence of hypernatraemia, we substitute varying amounts of 5% glucose-water for the 'fifth-normal saline', allow rather more than usual for the repair of existing deficits and aim at a somewhat less rapid correction of these deficits than in the ordinary case. Serum sodium levels vary so much, as do other features of these cases, that we think it unwise to lay down definite rules.

Summary

A brief review of the recent literature on the occurrence of hypernatraemic dehydration in infantile gastro-enteritis is followed by short accounts of two patients with this condition.

Analysis of the case records of 100 consecutive infants with gastro-enteritis whose serum electrolytes were determined reveals the following:

(1) An incidence of hypernatraemia similar to that reported from other centres;
(2) An association between hypernatraemia and the occurrence of neurological disturbances, similar to that reported by others, but neither as close nor as consistent as sometimes claimed;
(3) The importance of anorexia, fever and hyperventilation in the genesis of the condition.

Pathogenesis and treatment are briefly discussed.

REFERENCES

Bowie, M. D., McKenzie, D. and Hansen, J. D. L. (1958). Hyperosmolarity in infantile gastro-enteritis. *S. Afr. med. J.*, 32, 322.
Colle, E., Ayoub, E. and Raile, R. (1958). Hypertonic dehydration (hypernatremia): The role of feedings high in solutes. *Pediatrics*, 22, 5.
Cooke, R. E. (1959). Parenteral fluid therapy. In *Textbook of Pediatrics*, ed. Nelson, W. E., 7th ed., pp. 183-98. Saunders, Philadelphia and London.
—— and Ottenheimer, E. J. (1960). Clinical and experimental interrelations of sodium and the central nervous system. In *Advances in Pediatrics*, ed. Levine, S. Z., Vol. XI, pp. 81-145. The Year Book Publishers, Chicago.
Darrow, D. C. and Welsh, J. S. (1960). Recent experience in the treatment of diarrhea in infants. *J. Pediat.*, 56, 204.

Finberg, L. (1958). The possible role of the physician in causing hypernatremia in infants dehydrated from diarrhea. *Pediatrics*, **22**, 2.

—— and Harrison, H. E. (1955). Hypernatremia in infants. An evaluation of the clinical and biochemical findings accompanying this state. *Ibid.*, **16**, 1.

Franz, M. N. and Segar, W. E. (1959). The association of various factors and hypernatremic diarrheal dehydration. *Amer. J. Dis. Child.*, **97**, 298.

Harrison, H. E. and Finberg, L. (1959). Hypernatremic dehydration. *Pediat. Clin. N. Amer.*, Vol. 6, No. 1, p. 193.

Kerpel-Fronius, E. and Vönöczky, J. (1957). Significance of changes in the tonicity of body fluids in infantile diarrheal dehydration. *Ann. Paediat. Fenn.*, **3**, 403.

Rapoport, S. (1947). Hyperosmolarity and hyperelectrolyteria in pathologic conditions of childhood. *Amer. J. Dis. Child.*, **74**, 682.

Skinner, A. L. and Moll, F. C. (1956). Hypernatremia accompanying infant diarrhea. *Ibid.*, **92**, 562.

Tarail, R., Bass, L. W. and Runco, A. S. (1953). The frequency and nature of hypertonicity of the body fluids in infantile diarrhea. *Ibid.*, **86**, 658.

Weil, W. B. and Wallace, W. M. (1956). Hypertonic dehydration in infancy. *Pediatrics*, **17**, 171.

MYOCARDITIS AND CROUP CAUSED BY COXSACKIE VIRUS TYPE B5

BY

JUDITH M. BABB, MARGARET E. R. STONEMAN and H. STERN

From the Department of Paediatrics, St. George's Hospital and the Victoria Hospital for Children, and the Department of Virology, St. George's Hospital Medical School, London

(RECEIVED FOR PUBLICATION FEBRUARY 7, 1961)

Myocarditis has long been recognized as a complication of rheumatic fever, diphtheria, scarlet fever and whooping cough. It also occurs in association with poliomyelitis and more rarely with other virus infections such as influenza, mumps, psittacosis, infectious mononucleosis, primary atypical pneumonia, varicella, measles, infectious hepatitis and yellow fever (Lyon, 1956; Silber, 1958). Myocarditis has also been described as occurring without evidence of such primary disease and has then been labelled variously as Fiedler's, idiopathic, interstitial, isolated or aseptic myocarditis.

The association of myocarditis and pericarditis with epidemic pleurodynia was reported by Bing (1933) and Heckscher (1933). This disease was subsequently shown to be caused by infection with the Coxsackie group B viruses (Curnen, Shaw and Melnick, 1949). More recently these viruses have been incriminated as a cause of aseptic myocarditis in newborn infants and myocarditis and pericarditis in both children and adults.

In the newborn infant Coxsackie infections are usually severe and commonly fatal. The disease is generalized and the predominant lesion in most cases is cardiac, although many infants also show lesions in the central nervous system, liver, adrenals and other tissues. Outbreaks of neonatal myocarditis have occurred in maternity homes and nurseries at times of prevalence of Coxsackie infection in the general population. These have been reported from Johannesburg (Gear and Measroch, 1953; Javett, Heymann, Mundel, Pepler, Lurie, Gear, Measroch and Kirsch, 1956; Gear, 1958), Cape Town (Suckling and Vogelpoel, 1958; Simonhoff and Uys, 1958; Naudé, Selzer and Kipps, 1958; Kipps, Naudé, Don and Cooper, 1958), Southern Rhodesia (Montgomery, Gear, Prinsloo, Kahn and Kirsch, 1955), Amsterdam (Dekking, 1958; van Creveld and de Jager, 1956; Verlinde, van Tongeren and Kret, 1956), Czechoslovakia (Vaček, Lukes, Potuznik, Polodnikova and Vilim, 1959; Lukes, 1959) and Hungary (Dömök, Molnár and Rudnai, 1960). A similar outbreak but without virus confirmation occurred in a newborn nursery in Melbourne (French, 1953). Sporadic cases have been reported from the United States (Kibrick and Benirschke, 1956, 1958a; 1958b; Sabin, 1957; Benirschke, Kibrick and Craig, 1958; Benirschke and Pendleton, 1958; Newton and Hosier, 1958; Hosier and Newton, 1958; Sprunt, 1958; Sussman, Strauss and Hodes, 1959; Rapmund, Gauld, Rogers and Holmes, 1959; Moossy and Geer, 1960; Brown, Lenz and Agate, 1960; Woodward, McCrumb, Carey and Togo, 1960), Hawaii (Delaney and Fukunaga, 1958), the Transvaal (Gear, Measroch and Prinsloo, 1956) and Australia (Jack, 1958).

There have been fewer reports of myocarditis caused by Coxsackie group B viruses in older children and the disease has usually been less severe than in the newborn infant (McLean, Croft, Prince and Heckmann, 1957; Varcasia and Castelli, 1957; Kagan and Bernkopf, 1957; Hosier and Newton, 1958; McLean, Walker and McNaughton, 1960). Many of the older children present with pericarditis (Kagan and Bernkopf, 1957; McLean, Walker and Bain, 1958; Walker, McNaughton and McLean, 1959; Gordon, Lennette and Sandrock, 1959; Brodie and Marchessault, 1960; Woodward *et al.*, 1960), but this may be associated with clinical evidence of myocardial involvement (Kagan and Bernkopf, 1957).

In adults pericarditis has been the usual manifestation (Weinstein, 1957; Fletcher and Brennan, 1957, 1958; Movitt, Lennette, Mangum, Berk and Bowman, 1958; Bell and Meis, 1959; Gillett, 1959; Roberts, Lydon and MacIntosh, 1959; Sode and Baker, 1959; Woodward *et al.*, 1960) and some cases, as in children, have shown clinical evidence of severe myocardial damage (Null and Castle, 1959; Woodward *et al.*, 1960).

Coxsackie group A viruses may also be a cause of heart disease. Infection with these has been reported

in several cases of myocarditis in small children (Archetti and Bortolozzi, 1954; Hosier and Newton, 1958; de Góes, de Paola, Bruno-Lobo and Dias, 1959) and in a case of pericarditis in an adult (Movitt *et al.*, 1958).

Acute laryngo-tracheo-bronchitis or croup is of multiple aetiology. Most cases are caused by viruses, including influenza type A and the three parainfluenza viruses (Vargosko, Chanock, Huebner, Luckey, Kim, Cumming and Parrott, 1959) and Echo virus type 11 (Philipson and Wesslén, 1958). Apart from a mention that Coxsackie A9 may be a cause (Forbes, 1960) the Coxsackie viruses have not been incriminated so far in this type of respiratory infection.

During 1960 Coxsackie B infections were common in London (Stern, 1961). In the present paper four cases of severe infection in small children are described, two with myocarditis, one with myocarditis and croup and one with croup alone.

Virus Techniques

Virus Isolation. Throat swabs and faeces were dealt with at once or kept at −70° C. for 24 hours. The former were thoroughly rubbed into 1 ml. of Hanks' saline containing 500 units of penicillin, 200 μg. of streptomycin and 50 units of mycostatin per ml. and then spun at 2,000 r.p.m. for 15 minutes. Faecal specimens were emulsified with the Hanks' saline to make a 20% suspension and centrifuged at 4,000 r.p.m. for 30 minutes. Six tubes, comprising two Hela, two human primary amnion and two Rhesus monkey tissue cultures, were each inoculated with 0·2 ml. of supernatant from the treated throat swab or faeces. They were incubated at 37° C. for two hours and the fluid of each tube was then replaced with fresh medium. The tubes were examined microscopically for cytopathic changes daily for 14 days. In positive cases the fluid was removed and the virus identified by neutralization tests, usually in the type of tissue culture in which it was isolated.

The isolate was diluted one in 100 and mixed with equal volumes of antisera for each of the Coxsackie viruses B1 to 5 and A9, as well as with pools containing respectively all six Coxsackie antisera and the polio antisera. Antisera were prepared by hyperimmunization of rabbits and each serum was used at a dilution equivalent to 20 antibody units per 0·1 ml. The mixtures were kept at 37° C. for two hours and 0·2 ml. of each was inoculated into duplicate tissue culture tubes. A virus titration was included with each test. The results were read when the control tubes showed 4-plus cytopathic changes, usually within two to three days. When the results were equivocal because of excess virus the test was repeated using approximately 100 TCD_{50}.

The monkey kidney cells were maintained on medium 199 containing SV_5 antiserum, the Hela and amnion cells on Earle's saline with 0·5% lactalbumin hydrolysate and 5% inactivated horse serum. Refeeding of tubes was carried out at about five-day intervals and they were incubated without rolling.

Serology. Sera were obtained from patients during the acute and convalescent stages of illness and were stored at −20° C. until used. They were inactivated at 56° C. for half-an-hour and the two sera from each patient were tested at the same time.

Complement fixation tests for antibodies against influenza, parainfluenza and adenoviruses were carried out in tubes, using two units of complement, four units of antigen and overnight fixation at 4° C. Neutralization tests were used for the detection of Coxsackie antibodies. These were carried out by mixing equal volumes of several dilutions of each serum and virus suspensions containing approximately 100 TCD_{50} per 0·1 ml. They were kept at 37° C. for two hours and 0·2 ml. of each mixture was inoculated into duplicate tissue culture tubes. The results were read when control virus tubes showed 4-plus degeneration, usually within three to four days. Antibody titres were expressed as the reciprocal of the highest initial dilution of serum producing full fixation of complement or complete virus neutralization.

Case Reports

Case 1. A male child, 19 months old, weighed 3 lb. 11 oz. at birth. He was born prematurely at 36 weeks after induction for maternal toxaemia. He had pneumonia at 2 months of age and recurrent attacks of bronchitis subsequently. Two weeks before admission he had a further attack of pneumonia, treated with antibiotics, and since then had been having repeated attacks of dyspnoea.

On examination he was pale and showed slight peripheral oedema. The temperature was 98·6° F. The pulse rate was 120/min. and he had tic-tac heart sounds and a systolic murmur along the left sternal margin. The liver was enlarged to 3 cm. below the costal margin. The chest was clear.

Investigations showed a haemoglobin of 8 g./100 ml. and a white cell count of 8,400 with 38% neutrophils, 55% lymphocytes, 5% monocytes, 1% eosinophils and 1% basophils. The red cells were hypochromic with anisocytosis. The cold agglutinin and tuberculin skin tests were negative. A radiograph of the chest showed slight enlargement of the heart shadow. An electrocardiogram was normal. Phonocardiographic examination, three weeks after admission, demonstrated only physiological splitting of the second sound and a loud third sound. Faeces were examined for virus only three weeks after admission and no isolations were made. Serum specimens were obtained after the second and fifth weeks in hospital; both showed titres of more than 500 of Coxsackie B5 antibody. Antibodies against the other Coxsackie B viruses were all <5 in titre. The child had been vaccinated against poliomyelitis and low levels of antibodies for the three types were present.

He was treated with iron and one month later the haemoglobin level was 12·3 g./100 ml. One week after admission the signs of cardiac failure had disappeared and there were no further attacks of dyspnoea. He had

a mild attack of bronchitis two weeks later and a swab showed only normal bacterial flora. He was discharged five weeks after admission apparently well. Four months after the onset of his illness an apical systolic murmur was still present, but there were no signs of cardiac failure.

Eleven days after the child returned home his mother was admitted to hospital with aseptic meningitis and two days later his father and aunt, who lived in the same house, were also admitted with the same illness. Poliovirus type 3 was isolated from the mother's faeces and both parents showed high levels of polio type 3 antibody during convalescence. In both, Coxsackie B5 antibody was present at a titre of 5.

Case 2. The child, a male, weighed 5 lb. 2 oz. at birth. He was born at full term by normal delivery. He had always been difficult to feed, but was otherwise well until the age of 9 months when he was referred to hospital mainly on account of pallor.

On examination he was pale and had slight oedema of the legs. The temperature was 98·4° F. His pulse rate was 140/min. and he had tic-tac heart sounds and a systolic murmur at all areas of the praecordium and conducted into the axilla. The liver was enlarged to 3 cm. below the costal margin. The chest was clear.

Investigations showed a haemoglobin of 10·8 g./100 ml. and a white cell count of 12,400 with 21% neutrophils, 68% lymphocytes, 7% monocytes and 4% eosinophils. The red cells were slightly microcytic and hypochromic. The E.S.R. was 5 mm. in the first hour and the cold agglutinin test was negative. A radiograph of the chest and an electrocardiogram were both normal. A phonocardiogram demonstrated a mid-diastolic as well as a systolic murmur of ejection type. Coxsackie B5 was isolated from the faeces and the homologous antibody increased in titre from 5 to 100 during the course of illness.

He was treated with iron which increased his haemoglobin to 12 g./100 ml. after three weeks. Two weeks after admission he became pyrexial and had a slightly injected throat, but this cleared in four days without treatment. The signs of heart failure disappeared and he was discharged after one month in hospital. He still had a slight systolic murmur five months later.

Case 3. The infant, a 4-month-old male, weighed 5 lb. 6 oz. at birth. He was born prematurely at 36 weeks by caesarian section because of antepartum haemorrhage and was nursed for three days in an incubator. He made normal progress until one week before admission to hospital, when, after a second dose of triple antigen, he became lethargic. Three days later he became pyrexial and was diagnosed by his local doctor as a case of acute tonsillitis and treated with penicillin. For 24 hours before admission there had been anorexia and almost continuous screaming. His 3-year-old brother and parents were well.

On examination, he was a screaming, miserable, very pale child with conjunctivitis and injected fauces. The temperature was 102° F. The pulse rate was 170/min. and he had a blowing systolic murmur at all areas of the praecordium which was transmitted through to the back. The liver was enlarged to 3 cm. below the costal margin. There was a positive Kernig's sign but no neck stiffness.

The following day his condition was worse with marked respiratory stridor and apparently some difficulty in swallowing. There was oedema of the retropharyngeal space and enlarged glands in the left posterior triangle.

Laboratory investigations showed a haemoglobin of 8·6 g./100 ml., a white cell count of 13,300 with 48% neutrophils and 52% lymphocytes, a normal urine and cerebrospinal fluid and a negative Paul-Bunnell test. A radiograph of the chest was normal. Bacteriological examination of throat and eye swabs and faeces showed only normal flora. Coxsackie virus type B5 was isolated from the throat swab. Type B5 antibodies increased in titre during the course of the illness from five to 50. Antibodies against influenza viruses types A, B and C, parainfluenza viruses types 1, 2 and 3 and adenoviruses were absent.

The infant was treated with oxygen, humidity and tetracycline, and improved rapidly. An electrocardiogram on the eleventh day after admission was normal. The heart murmur became softer and by the twelfth day had disappeared. He was apparently completely well on discharge and again five months later.

Case 4. A male infant, aged 4 months, weighed 7 lb. 12 oz. at birth. He was born by low forceps delivery and made normal progress until 12 weeks before admission when he developed a spasmodic cough which was worse at night. He produced mucoid sputum, but there was no whooping or vomiting. Soon after developing the cough he became obviously wheezy.

On examination his temperature was 99·4° F. There was marked inspiratory stridor. The tonsils and posterior pharyngeal wall were injected and the former were covered with patchy exudate. The cervical glands were bilaterally enlarged. The heart sounds were normal and the chest was clear. The liver was slightly enlarged.

The haemoglobin was 13·1 g./100 ml. and the white cell count was 10,900 with 28% neutrophils, 64% lymphocytes, 6% monocytes and 2% eosinophils. Radiograph of the chest was normal. Bacteriological examination of the throat showed only normal flora. Coxsackie B5 was isolated from the faeces. An acute serum specimen was not taken, but a specimen collected on the 14th day showed a Coxsackie B5 antibody titre of 50. Antibodies were absent against influenza types A, B and C, parainfluenza types 1, 2 and 3 and adenoviruses.

He was treated with oxygen, humidity and tetracycline. Despite this, four days after admission, his condition deteriorated and he showed extreme respiratory distress. There was severe stridor, with suprasternal and intercostal recession with poor entry and the pulse rate had increased to 140/min. A tracheotomy was performed and laryngoscopy showed slightly injected and oedematous vocal cords. He improved rapidly and had been well since, but oedema of his larynx has persisted and after

three months it has not been possible to close his tracheotomy.

Discussion

The majority of cases of aseptic myocarditis which have been reported since the original observations of Fiedler (1899) and Zuppinger (1901) have been within the age range of 3 months to 3 years: Saphir and Cohen (1957) reviewed 90 cases which came to autopsy after 1948 and showed that 71% were under 1 year old. Although the disease tends to be less severe in older children than in newborn infants, epidemics have been described in older children which have carried a high mortality (Stoeber, 1952; Choremis, Cassimos, Nihoyannopoulos, Mavrou and Haka, 1956; Freundlich, Berkowitz, Elkon and Wilder, 1958). The present paper shows that at least a proportion of the cases of myocarditis in older children is caused by Coxsackie group B viruses.

The first two cases in the present series were very similar in their clinical features, although their manner of onset was different. Case 1 presented with paroxysmal dyspnoea after a respiratory infection, whereas Case 2 was referred to the outpatient department owing to pallor. On examination both were pale and showed cardiac failure with peripheral oedema, tachycardia, systolic murmurs and liver enlargement. The degree of anaemia in Case 1 was at first thought to be sufficient to account for the cardiac failure. However, when the second case was observed with the same features, but only mild anaemia, the diagnosis of virus myocarditis was considered and later confirmed by virus studies.

These two children resembled in their clinical features other reported cases of Coxsackie B myocarditis of older children. Varcasia and Castelli (1957) described a 2½-year-old boy also with a B5 infection. He presented with dyspnoea and pallor accompanying an upper respiratory infection and examination showed mild anaemia and cardiac failure including cardiac enlargement and a transient systolic murmur. Myocardial involvement was confirmed by electrocardiographic changes. Follow-up studies were not available. The 5-year-old boy reported by both McLean *et al.* (1957) and Hosier and Newton (1958), with Coxsackie B2 infection, had signs of cardiac failure two weeks after an upper respiratory illness. Gross cardiac enlargement was demonstrated radiologically and his electrocardiographic changes were compatible with myocarditis. He had two relapses during the course of his illness and the cardiomegaly persisted for at least 10 months.

Kagan and Bernkopf reported a more severe infection in a 10-month-old girl. She was very ill with cyanosis and severe pallor and evidence of gross cardiac failure. A large pericardial effusion developed and Coxsackie B3 was isolated both from the effusion and faeces. Cardiac enlargement persisted despite aspiration of the pericardial fluid, but recovery was complete after 43 days. They observed 12 other cases of acute myocarditis during the same period. These, aged 5 months to 9 years, had similarly severe degrees of cardiac failure and five of the children died; virus was isolated from the myocardium of two of them. The 7-week-old infant also reported by Hosier and Newton died after a fulminating course similar to that occurring in newborn infants.

The third case of the present group was admitted to hospital with acute respiratory infection. On examination he was found to have signs of cardiac failure. Twenty-four hours later he developed laryngeal stridor. In Case 4 severe laryngeal stridor necessitating tracheotomy was the main symptom. These appear to be the first reported cases of croup caused by Coxsackie B viruses. The association of croup with myocarditis was previously recorded by Saphir (1945), although virus studies were not available; five children, aged 11 months to 7 years, died despite tracheotomy and the cause of death was considered to have been the severe myocarditis demonstrated at autopsy.

The absence of electrocardiographic changes in the present cases of myocarditis was possibly due to examination in the later stages of illness. Absence of such changes, however, does not exclude myocarditis (Fox and Overstreet, 1941; Lyon, 1956; Delaney and Fukunaga, 1958). The final prognosis is unknown. Cases 1 and 2 showed persistent heart murmurs four and five months later. Repair of the damaged myocardium in neonatal cases is by fibrosis (Simenhoff and Uys, 1958) and it is uncertain what part the fibrous lesions may play in heart disease in later life.

With the increasing use of routine virological investigations it is likely that the aetiology of more cases of aseptic myocarditis will be discovered. All members of the enterovirus group can probably cause cardiac damage. Both group A and group B Coxsackie viruses have now been shown to be capable of doing so and the polio viruses have long been recognized as a cause of myocarditis in a high proportion of cases of paralytic poliomyelitis (Nordenstam, 1956; Bengtsson and Nordenstam, 1956). The demonstration of electrocardiographic changes during an epidemic of aseptic meningitis caused by Echo virus type 9 (von Olderhausen, 1957) suggests that the Echo viruses may also be responsible for some cases of myocarditis.

Summary

Previous reports of myocarditis due to Coxsackie virus infections are briefly reviewed.

Four cases are described of Coxsackie virus B5 infection in children aged 4 to 19 months. These occurred during a period of prevalence of Coxsackie infection in the general population. Two of the cases had clinical evidence of acute myocarditis, one of myocarditis with croup, and the fourth of croup alone. All the patients recovered.

The two children with croup are, we believe, the first reported cases of croup due to Coxsackie virus infection.

We would like to thank Dr. Ursula James of the Victoria Hospital for Children for allowing us to publish her cases and for her helpful advice and criticism. We are also grateful to Professor S. D. Elek of St. George's Hospital for his advice on the virological details.

References

Archetti, I. and Bortolozzi, M. (1954). Un virus del tipo Coxsackie isolato durante un'epidemia clinicamente non precisata. (Nota preliminare.) *R.C. Ist. sup. Sanità (Roma)*, **17**, 999.

Bell, J. F. and Meis, A. (1959). Pericarditis in infection due to Coxsackie virus group B, type 3. *New Engl. J. Med.*, **261**, 126.

Bengtsson, E. and Nordenstam, H. (1956). The poliomyelitis epidemic in Stockholm, 1953. XV. Cardiovascular complications in fatal cases of poliomyelitis. *Acta med. scand.*, Suppl. 316, 95.

Benirschke, K., Kibrick, S. and Craig, J. M. (1958). The pathology of fatal Coxsackie infection in the newborn. *Amer. J. Path.*, 34, 587.

—— and Pendleton, M. E. (1958). Coxsackie virus infection. An important complication of pregnancy. *Obstet. and Gynec.*, 12, 305.

Bing, H. I. (1933). Epidemical pericarditis. *Acta med. scand.*, 80, 29.

Brodie, H. R. and Marchessault, V. (1960). Acute benign pericarditis caused by Coxsackie virus group B. *New Engl. J. Med.*, 262, 1278.

Brown, G. C., Lenz, W. R. and Agate, G. H. (1960). Laboratory data on the Detroit poliomyelitis epidemic—1958. *J. Amer. med. Ass.*, 172, 807.

Choremis, C., Cassimos, Ch., Nihoyannopoulos, J., Mavrou, K. and Haka, C. (1956). Idiopathic myocarditis of the Fiedler type. *Ann. paediat. (Basel)*, **187**, 444.

van Creveld, S. and de Jager, H. (1956). Myocarditis in newborns caused by Coxsackie virus. Clinical and pathological data. *Ibid.*, **187**, 100.

Curnen, E. C., Shaw, E. W. and Melnick, J. L. (1949). Disease resembling nonparalytic poliomyelitis associated with a virus pathogenic for infant mice. *J. Amer. med. Ass.*, **141**, 894.

de Góes, P., de Paola, D., Bruno-Lobo, M. and Dias, L. D. (1959). Miocardite por vírus Coxsackie do grupo A. *An. Microbiol. (rio de J.)*, 7, 13.

Dekking, F. (1955). Myocarditis bij zuigelingen veroorzaakt door het Coxsackie virus type B. *Ned. T. Geneesk*, **99**, 2676.

Delaney, T. B. and Fukunaga, F. H. (1958). Myocarditis in a newborn infant with encephalomeningitis due to Coxsackie virus group B, type 5. *New Engl. J. Med.*, **259**, 234.

Dömök, I., Molnár, E. and Rudnai, O. (1960). An epidemic of Bornholm's disease in Hungary in 1958. *Acta microbiol. Acad. Sci. hung.*, 7, 151.

Fiedler, A. (1899). Ueber akute interstitielle myokarditis. Festschr. der Stadkrankenh. Dresden Friedrichstadt; part 2, 3.

Fletcher, E. and Brennan, C. F. (1957). Cardiac complications of Coxsackie-virus infection. *Lancet*, **1**, 913.

—— —— (1958). Cardiac complications of Coxsackie-virus infection. *Ibid.*, 2, 585.

Forbes, J. A. (1960). Croup viruses: clinical aspects. *Med. J. Aust.*, 769.

Fox, I. R. and Overstreet, R. M. (1941). Isolated myocarditis: report of a case. *Northw. Med. (Seattle)*, **40**, 89.

French, E. L. (1953). Personal communication. Quoted by Kibrick and Benirschke (1956).

Freudlich, E., Berkowitz, M., Elkon, A. and Wilder, A. (1958). Primary interstitial myocarditis. Report of an epidemic outbreak. *Amer. J. Dis. Child.*, **96**, 43.

Gear, J. H. S. (1958). Coxsackie virus infections of the newborn. In *Progress in Medical Virology*, ed. E. Berger and J. L. Melnick, vol. 1, p. 106. Karger, Basel.

—— and Measroch, V. (1953). *S. Afr. Inst. med. Res. Ann. Rep. for* 1952, p. 38.

——, —— and Prinsloo, F. R. (1956). The medical and public health importance of the Coxsackie viruses. *S. Afr. med. J.*, **30**, 806.

Gillett, R. L. (1959). Acute benign pericarditis and the Coxsackie viruses. *New Engl. J. Med.*, **261**, 838.

Gordon, R. B., Lennette, E. H. and Sandrock, R. S. (1959). The varied clinical manifestations of Coxsackie virus infections: observations and comments on an outbreak in California. *Arch. intern. Med.*, **103**, 63.

Heckscher, H. (1933). Myositis epidemica-Sorositis. *Acta med. scand.*, **80**, 251.

Hosier, D. M. and Newton, W. A., Jr. (1958). Serious Coxsackie infection in infants and children. *Amer. J. Dis. Child.*, **96**, 251.

Jack, I. (1958). Personal communication. Quoted by Kibrick and Benirschke (1958b).

Javett, S. N., Heymann, S., Mundel, B., Pepler, W. J., Lurie, H. I., Gear, J., Measroch, V. and Kirsch, Z. (1956). Myocarditis in the newborn infant. A study of an outbreak associated with Coxsackie group B virus infection in a maternity home in Johannesburg. *J. Pediat.*, **48**, 1.

Kagan, H. and Bernkopf, H. (1957). Pericarditis caused by Coxsackie virus B. *Ann. paediat. (Basel)*, **189**, 44.

Kibrick, S. and Benirschke, K. (1956). Acute aseptic myocarditis and meningoencephalitis in the newborn child infected with Coxsackie virus group B, type 3. *New Engl. J. Med.*, **255**, 883.

——, —— (1958a). Severe generalized disease in the newborn due to Coxsackie virus group B. *Amer. J. Dis. Child.*, **96**, 498.

——, —— (1958b). Severe generalized disease (encephalohepatomyocarditis) occurring in the newborn period and due to infection with Coxsackie virus, group B. Evidence of intrauterine infection with this agent. *Pediatrics*, **22**, 857.

Kipps, A., Naudé, W. du T., Don, P. and Cooper, E. D. (1958). Coxsackie virus myocarditis of the newborn. Epidemiological features. *Med. Proc.*, **4**, 401.

Lukes, J. (1959). Newborn myocarditis and meningoencephalitis of Coxsackie virus B3 origin. *Čsl. Pediat.*, **14**, 731.

Lyon, E. (1956). *Virus Diseases and the Cardiovascular System.* Grune and Stratton, New York and London.

McLean, D. M., Croft, C. C., Prince, J. T. and Heckmann, E. E. (1957). Coxsackie and Echo virus infections in Ohio during 1956. *Ohio St. med. J.*, **53**, 907.

——, Walker, S. J. and Bain, H. W. (1958). Coxsackie B5 virus in association with pericarditis and pleurodynia. *Canad. med. Ass. J.*, **79**, 789.

——, —— and McNaughton, G. A. (1960). Enterovirus infections in Toronto, 1959. *Ibid.*, **82**, 661.

Montgomery, J., Gear, J., Prinsloo, F. R., Kahn, M. and Kirsch, Z. G. (1955). Myocarditis of the newborn. An outbreak in a maternity home in Southern Rhodesia associated with Coxsackie group-B virus infection. *S. Afr. med. J.*, **29**, 608.

Moossy, J. and Geer, J. C. (1960). Encephalomyelitis, myocarditis and adrenal cortical necrosis in Coxsackie B3 virus infection. Distribution of the central nervous system lesions. *Arch. Path. (Chicago)*, **70**, 614.

Movitt, E. R., Lennette, E. H., Mangum, J. F., Berk, M. and Bowman, M. S. (1958). Acute benign pericarditis: report of two cases associated with group A and group B Coxsackie viruses. *New Engl. J. Med.*, **258**, 1082.

Naudé, W. du T., Selzer, G. and Kipps, A. (1958). Coxsackie virus myocarditis of the newborn. Virus studies. *Med. Proc.*, **4**, 397.

Newton, W. A., Jr. and Hosier, D. M. (1958). Coxsackie infection in infants and children: focal and disseminated; fatal and non-fatal. *Amer. J. Path.*, **34**, 587.

Nordenstam, H. (1956). The poliomyelitis epidemic in Stockholm 1953. XIX. Patho-anatomical findings in 26 fatal cases of poliomyelitis. *Acta med. scand.*, Suppl. 316, 114.

Null, F. C., Jr. and Castle, C. H. (1959). Adult pericarditis and myocarditis due to Coxsackie virus group B, type 5. *New Engl. J. Med.*, **261**, 937.

von Olderhausen, H.-F. (1957). Klinische Beobachtungen über eine neuartige primäre aseptische Meningoenzephalitis. *Dtsch. med. Wschr.*, **82**, 442.

Philipson, L. and Wesslén, E. (1958). Recovery of a cytopathogenic agent from patients with non-diphtheritic croup, and from day-nursery children. I. Properties of the agent. *Arch. ges. Virusforsch.*, **8**, 77.

Rapmund, G., Gauld, J. R., Rogers, N. G. and Holmes, G. E. (1959). Neonatal myocarditis and meningoencephalitis due to Coxsackie virus group B, type 4. Virologic study of a fatal case with simultaneous aseptic meningitis in the mother. *New Engl. J. Med.*, **260**, 819.

Roberts, R., Lydon, M. and MacIntosh, M. (1959). Coxsackie pericarditis. *Canad. med. Ass. J.*, **80**, 722.

Sabin, A. (1957). Comment in *Year Book of Pediatrics* (1957-58 Year Book Series), ed. S. S. Gellis, p. 269. The Yearbook Publishers, Chicago.

Saphir, O. (1945). Laryngeal edema, myocarditis and unexpected death (early acute laryngotracheobronchitis). *Amer. J. med. Sci.*, **210**, 296.

—— and Cohen, N. A. (1957). Myocarditis in infancy. *A.M.A. Arch. Path.*, **64**, 446.

Silber, E. N. (1958). Respiratory viruses and heart disease. *Ann. intern. Med.*, **48**, 228.

Simenhoff, M. L. and Uys, C. J. (1958). Coxsackie virus myocarditis of the newborn. A pathological survey of 4 cases. *Med. Proc.*, **4**, 389.

Sode, J. and Baker, W. J. (1959). Acute benign pericarditis and pneumonitis associated with Coxsackie virus group B, type 2, infection in a young man. *Arch. intern. Med.*, **104**, 313.

Sprunt, K. (1958). Personal communication. Quoted by Sussman *et al.* (1959).

Stern, H. (1961). Aetiology of central nervous system infections during period of prevalence of poliovirus and Coxsackie virus. *Brit. med. J.*, **1**, 1061,

Stoeber, E. (1952). Weitere Untersuchungen über epidemische Myocarditis ('Schwielenherz') des Säuglings. *Z. Kinderheilk.*, **71**, 319, 592.

Suckling, P. V. and Vogelpoel, L. (1958). Coxsackie myocarditis of the newborn. *Med. Proc.*, **4**, 372.

Sussman, M. L., Strauss, L. and Hodes, H. L. (1959). Fatal Coxsackie group B virus infection in the newborn. *Amer. J. Dis. Child.*, **97**, 483.

Vanek, J., Lukes, J., Potuznik, V., Polodnikova, I. and Vilim, V. (1959). Myocarditis and encephalitis in newborn infants caused by Coxsackie B virus. *J. Hyg. Epidem. (Praha)* **3**, 283.

Varcasia, E. and Castelli, L. (1957). Su di un caso di miocardite da Coxsackie B5. *R.C. Ist. sup. Sanità*, **20**, 831.

Vargosko, A. J., Chanock, R. M., Huebner, R. J., Luckey, A. H., Kim, H. W., Cumming, C. and Parrott, R. H. (1959). Association of type 2 hemadsorption (parainfluenza 1) virus and Asian influenza A virus with infectious croup. *New Engl. J. Med.*, **261**, 1.

Verlinde, J. D., van Tongeren, H. A. E. and Kret, A. (1956). Myocarditis in newborns due to group B Coxsackie virus. Virus studies. *Ann. paediat. (Basel)*, **187**, 113.

Walker, S. J., McNaughton, G. A. and McLean, D. M. (1959). Coxsackie B5 virus infections in children: Toronto, 1958. *Canad. J. publ. Hlth*, **50**, 461.

Weinstein, S. B. (1957). Acute benign pericarditis associated with Coxsackie virus group B, type 5. *New Engl. J. Med.*, **257**, 265.

Woodward, T. E., McCrumb, F. R., Jr., Carey, T. N. and Togo, Y. (1960). Viral and rickettsial causes of cardiac disease, including the Coxsackie virus etiology of pericarditis and myocarditis. *Ann. intern. Med.*, **53**, 1130.

Zuppinger (1901). Ueber Herztod bei anscheinend bedeutungslosen Oberflächlichen Geschwürsprocessen. *Wien. klin. Wschr.*, **14**, 799.

CONTUSION OF THE LUNG IN CHILDHOOD

BY

A. SCHWARTZ and J. B. BORMAN

From the Departments of Diagnostic Radiology and Thoracic Surgery, Hadassah University Hospital, Jerusalem, Israel

(RECEIVED FOR PUBLICATION MARCH 24, 1961)

Chest injuries are on the increase in all civilized countries, mainly due to the rising number of traffic accidents (Zenker, 1956; Daughtry, 1957; Strug, Glass, Leon and Salatich, 1960).

The clinical picture of severe chest trauma, both penetrating (Gray, Harrison, Couves and Howard, 1960) and blunt (Harrison, Gray, Couves and Howard, 1960; Griffiths, 1960), has been amply described. Lesser injuries, however, have been neglected in the literature, although these cases often have radiological evidence of lung damage. This is particularly so in children, in whom the pulmonary changes may be overlooked because of the paucity of clinical symptoms. The purpose of this paper is to describe four cases of blunt chest injury in children and to discuss the symptomatology and radiological appearance of this condition.

Case Reports

Case 1. An 8-year-old boy fell, head down, from a height of 5 metres. He was unconscious following the accident and on admission one and a half hours later was still semi-conscious. Temperature was 37° C., pulse 130/min. and respiration 44/min. A skull radiograph showed no fracture, but air was noted in the soft tissues of the neck and a radiograph of the chest was obtained. This showed a pneumomediastinum and shadowing of the left mid-lung field with a rounded translucent area containing a fluid level (Fig. 1). No rib fractures were noted, and there was no pneumothorax and no fluid in the pleural cavity.

The diagnosis of contusion of the lung and pneumomediastinum was made. On antibiotic therapy the child's general condition improved. The shadow in the left lung resolved rapidly and when discharged eight days after his injury the only abnormal x-ray finding consisted of a residual ring shadow 2 cm. in diameter (Fig. 2).

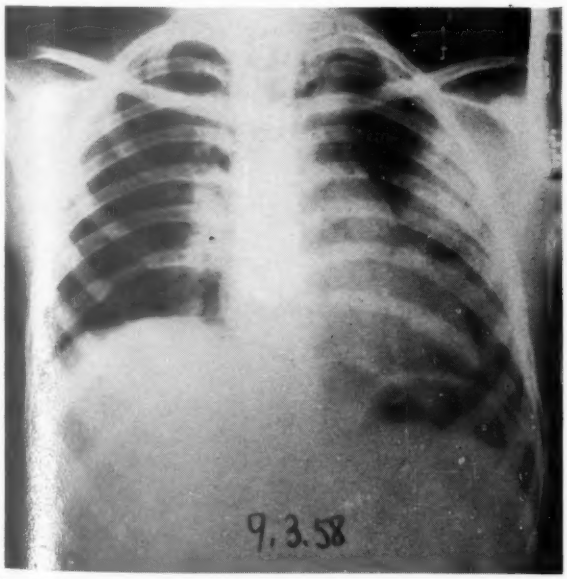


FIG. —Case 1: Postero-anterior radiograph of the chest showing air in the mediastinum extending into the neck. Note the air outlining the left border of the descending aorta. Radiolucent area with fluid level visible in the opacity in the left middle lung field.

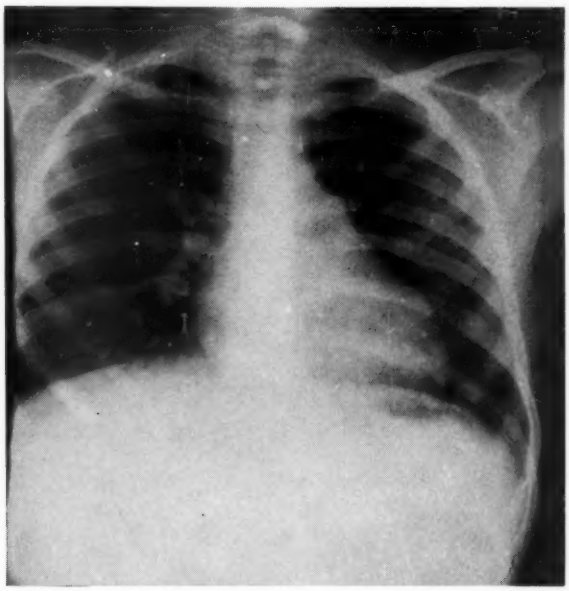


FIG. 2.—Case 1: Eight days later the only abnormal finding is a ring shadow, 2 cm. in diameter, at the site of the previous opacity.

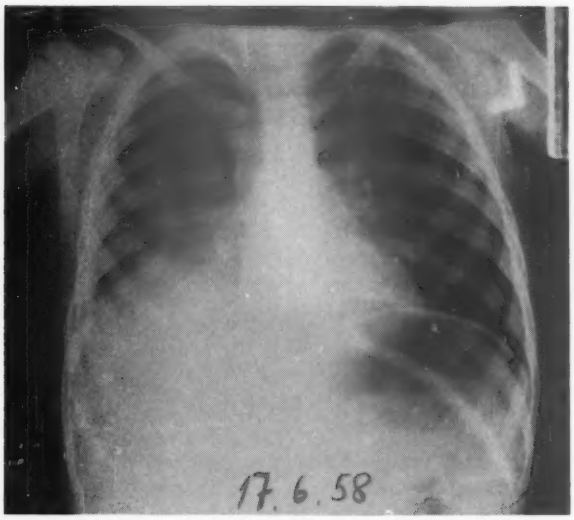


FIG. 3.—Case 2: Radiograph, taken on admission, showing a dense opacity obscuring the right diaphragm.

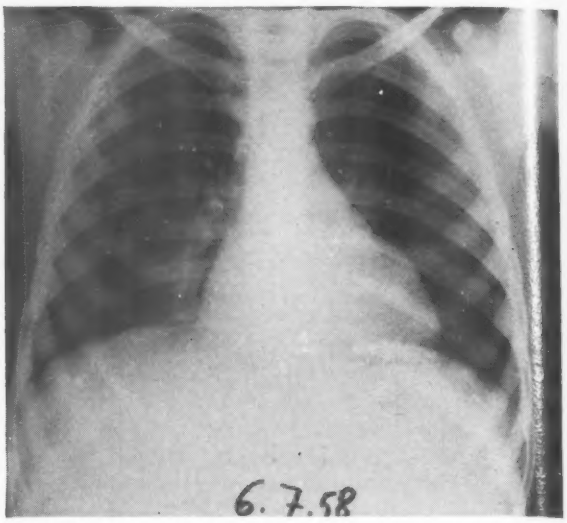


FIG. 4.—Case 2: Radiograph 19 days later shows minimal residual density adjacent to the right border of the heart.

Case 2. An 8-year-old girl was admitted 24 hours after having been knocked down by a motor car. On admission she complained of pain in the right upper abdomen. She had no cough, haemoptysis or dyspnoea. Examination revealed a pale child with a normal blood pressure but with a pulse of 160/min. and a temperature of 40° C. Crepitations were heard over both lung bases. She had a bilateral Babinsky reflex. A skull radiograph was normal. A chest radiograph revealed a density in the right lower lung field obscuring the diaphragm. No rib fracture could be detected. The rest of the lung fields were normal (Fig. 3). The opacity in the right chest was interpreted as contusion of the lung.

Treatment with penicillin and streptomycin resulted in a gradual decline of the fever accompanied by clearing of the lung. On discharge 19 days after injury the lung shadow had cleared almost completely (Fig. 4).

Case 3. A 4-year-old boy was admitted as an emergency following a fall on to his left chest. On examination he was pale, but not in distress. Blood pressure and respiration were normal, pulse 120/min. and tem-

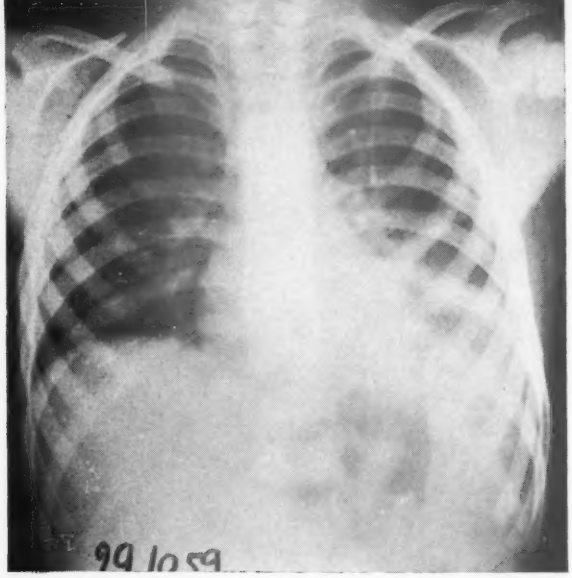


FIG. 5.—Case 3: Radiograph taken on admission showing haziness of the left lower lung field with blurring of the diaphragm.

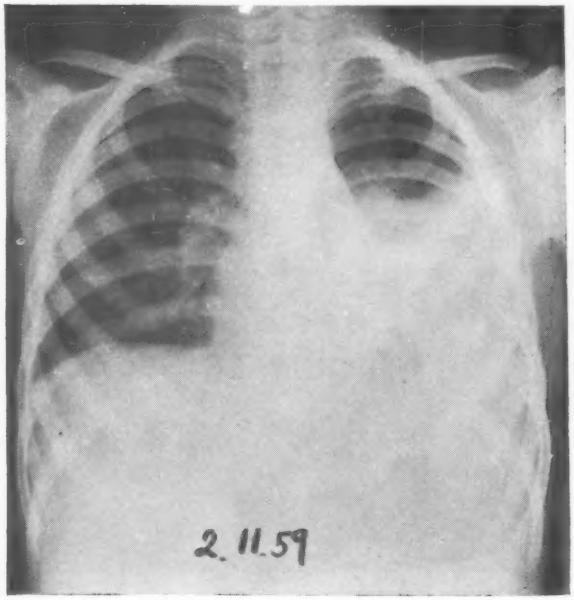


FIG. 6.—Case 3: Three days after admission the density, now occupying the lower half of the left hemithorax, is typical of intrapleural fluid.

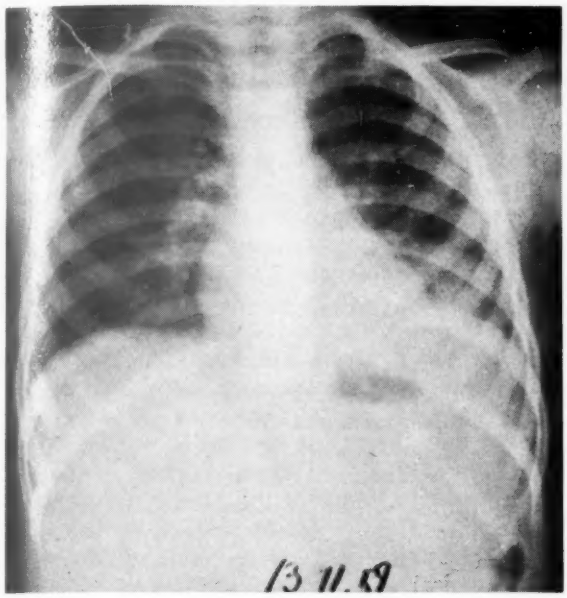


FIG. 7.—Case 3: Radiograph on the day of discharge shows only slight residual clouding at left base.

perature 37° C. Dullness and diminished air entry were found at the left base.

Chest radiograph showed a broad belt of haziness in the left lower lung field obscuring the diaphragm. There was a suggestion of fluid in the left costophrenic sinus. No pneumothorax or rib fracture was detected (Fig. 5).

The diagnosis of contusion of the lung with haemothorax was made.

Antibiotic therapy was immediately commenced, but the temperature rose for the next three days. A chest film at this time showed a dense shadow occupying the lower half of the left hemithorax (Fig. 6). Pleural tap was done and 60 ml. of dark blood removed. A chest radiograph taken after this showed only slight reduction in the size of the shadow, suggesting that the greater part of it was due to intrapulmonary pathology.

The antibiotic therapy was continued and the temperature gradually settled. When discharged 16 days after admission the lungs, clinically and radiologically, had almost cleared (Fig. 7). The child remained symptom-free on follow-up examination one month after discharge.

Case 4. A 12-year-old boy was rushed to the emergency room after being sandwiched between two cars, and sustaining a crushing injury to his chest.

Examination revealed a frightened, pale boy, not in shock. Blood pressure was 125/70 mm. Hg, pulse 90/min. and temperature 38° C. No abnormal findings could be detected in the lungs. Tyre pressure marks were present on the anterior and posterior chest walls.

A radiograph of the chest showed a widened mediastinum with an ill-defined left border. There were nodular densities scattered throughout the left lung

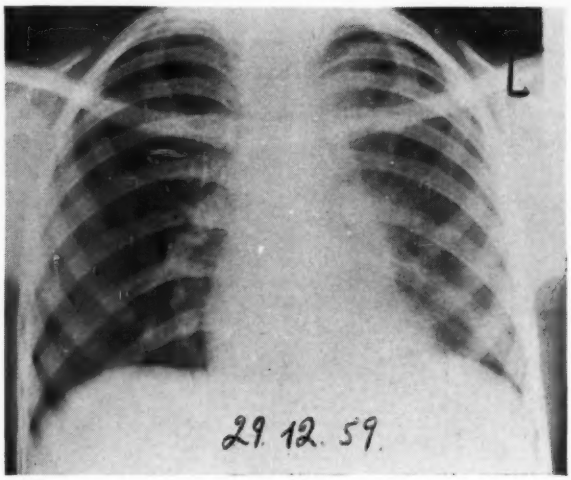


FIG. 8.—Case 4: Radiograph on admission showing widening of the mediastinum with blurring of its left border, small densities scattered in the left lung field and a tiny apical pneumothorax.

and a tiny left apical pneumothorax was noted (Fig. 8). No fracture of the ribs or sternum was detected.

Contusion of the lung with mediastinal haematoma was diagnosed. He received penicillin and streptomycin and the temperature returned to normal within three days. A chest film on the third day after admission showed increased mediastinal widening, fluid in the left pleural cavity and confluence of the nodular densities in the left lower lung field (Fig. 9). Subsequent radiographs showed gradual decrease of the mediastinal shadow, resorption of the fluid, clearing of the lung field and disappearance of the pneumothorax.

When discharged two weeks after his accident his chest was clinically and radiographically normal and remained so on follow-up examination two months later (Fig. 10).

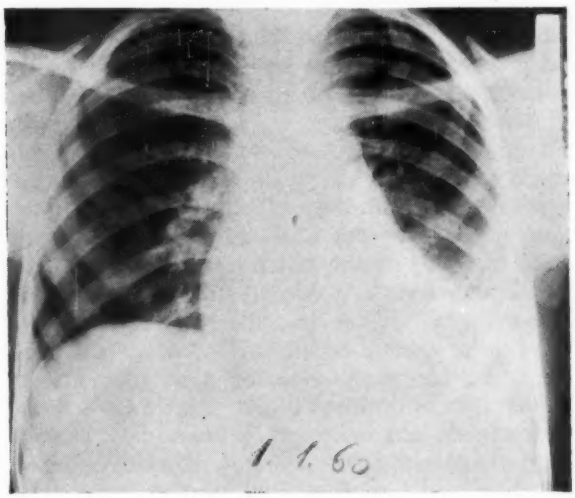


FIG. 9.—Case 4: Three days later the mediastinum is still wide, but its left border is now distinct. Fluid is present in the left pleural cavity.

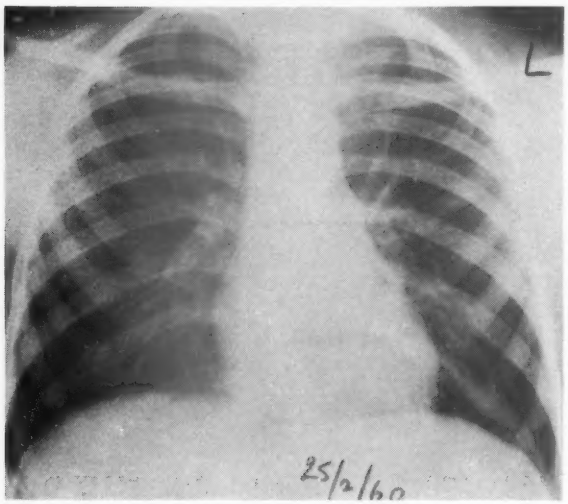


FIG. 10.—Case 4: Two months after injury the chest is normal.

Discussion

Blunt chest injury in children differs in its symptomatology from that occurring in adults. This is due to the elasticity of the thoracic cage in the former, which allows a blunt injury to contuse and even lacerate the lung and/or other intrathoracic organs without fracturing a rib (Wilson, 1943). Because of the absence of a rib fracture the injured child may not complain of pain in the chest, and consequently a chest radiograph is often omitted. The clinical signs of injury to the lung being minimal, or even absent, attention may be drawn to a concomitant injury. Two of our cases were admitted because of head injuries. In one of them a chest radiograph was not requested on admission (Case 1) and a pulmonary injury was only detected by the presence of air in the soft tissues of the neck as seen on the skull radiograph. Haemoptysis, dyspnoea and cough, the expected findings accompanying lung damage, were absent in our cases. This is at variance with the findings of Sealy (1949) who found haemoptysis in 35 out of 40 adults with contusion of the lung due to non-penetrating injury.

It is therefore a good rule to obtain a chest radiograph if possible in the upright position, of every child after a deceleration type of accident, even in the absence of signs of injury to the chest. Radiographs of the chest in our cases did not reveal rib fractures, but evidence of pulmonary damage was seen in all of them. Fracture of a rib, however, is probably an important indication that the child has received a severe blow. During the period of time the four cases were observed, two other children were admitted with fractured ribs as a result of traffic accidents. Both of them had extensive haemopneumothorax with contusion of the lung. Interestingly, they, too, had no cough or haemoptysis despite the severe trauma to the lung.

The radiographic changes after a blunt injury without rib fracture are variable and depend upon the intrathoracic organ injured. If only the lung is injured, as in these cases, fuzzy opacities of different size and density with irregular borders are the principal findings (Westermark, 1941). A pneumothorax or haemothorax or both may be present. The mediastinum is occasionally widened and pneumomediastinum may be evident. Subcutaneous emphysema in the neck and chest wall may be seen with, or without, pneumothorax (Vandooren, 1958). Extensive, increasing subcutaneous emphysema should arouse the suspicion of a tear or rupture of the trachea or bronchus. A high diaphragm on the injured side and dilatation of the stomach is of common occurrence (Virshup, 1960).

The underlying pathology causing the intrapulmonary opacities is still uncertain. The possible causes of the lung shadows appearing in the radiograph are interstitial haematoma (Major, 1956), acute localized oedema (Zenker, 1956; Barrett, 1960), patchy confluent atelectasis (Major, 1956), and intra-alveolar haemorrhage (Sealy, 1949). Probably all the above factors play some part in the production of the lung opacities.

These pulmonary contusions, *per se*, do not require surgical intervention. Treatment should be directed primarily towards concomitant injuries if present, e.g. multiple fractures, rupture of spleen or other abdominal viscera and head injuries. Children with lung contusion alone should receive prophylactic antibiotic therapy, as infection may complicate these injuries (Fallon, 1940; Phillips, 1947). They should be kept under observation in hospital until the lungs are clear. This generally occurs within three weeks (Sealy, 1949; Westermark, 1941; Greening, Kynette and Hodes, 1957).

Our cases had some fever during the first few days, but on antibiotic treatment the temperature settled. None of them developed frank pneumonia, abscess or bronchiectasis and the final follow-up examination showed clinically and radiologically normal lungs. Cases have been described which developed round or ring shadows persisting for as long as three months (Greening *et al.*, 1957). Pulmonary haematoma due to blunt injury may occasionally persist even longer and masquerade as a coin lesion. Such cases have undergone thoracotomy (Salyer, Blake and Forsee, 1953).

Summary

The clinical picture and radiological appearance of lung contusion in children after blunt injuries to the chest is described. Illustrative cases are presented.

There is a discrepancy between the minimal clinical findings and the marked x-ray changes of the lung.

A chest film should be obtained of all children involved in deceleration accidents even in the absence of symptoms and signs pointing to chest injury.

References

Barrett, N. R. (1960). Early treatment of stove-in chest. *Lancet*, 1, 293.

Daughtry, D. C. (1957). Management of nonpenetrating thoracic injuries. *Amer. Surg.*, **23**, 462.

Fallon, M. (1940). Lung injury in the intact thorax: with report of a case. *Brit. J. Surg.*, **28**, 39.

Gray, A. R., Harrison, W. H., Jr., Couves, C. M. and Howard, J. M. (1960). Penetrating injuries to the chest. Clinical results in the management of 769 patients. *Amer. J. Surg.*, **100**, 709.

Greening, R., Kynette, A. and Hodes, P. J. (1957). Unusual pulmonary changes secondary to chest trauma. *Amer. J. Roentgenol.*, **77**, 1059.

Griffiths, H. W. C. (1960). Crush injuries of the chest. *J. roy. Coll. Surg. Edinb.*, **6**, 13.

Harrison, W. H., Jr., Gray, A. R., Couves, C. M. and Howard, J. M. (1960). Severe non-penetrating injuries to the chest. Clinical results in the management of 216 patients. *Amer. J. Surg.*, **100**, 715.

Major, H. (1956). Der posttraumatische Lungenkollaps. *Arch. klin. Chir.*, **284**, 177.

Phillips, E. (1947). Pneumonia following nonpenetrating pulmonary injuries. *J. Amer. med. Ass.*, **133**, 161.

Salyer, J. M., Blake, H. A. and Forsee, J. H. (1953). Pulmonary hematoma. *J. thorac. Surg.*, **25**, 336.

Sealy, W. C. (1949). Contusions of the lung from nonpenetrating injuries to the thorax. *Arch. Surg.* (*Chicago*), **59**, 882.

Strug, L. H., Glass, B., Leon, W. and Salatich, M. (1960). Severe crushing injuries of the chest. A simple method of stabilization. *J. thorac. Surg.*, **39**, 166.

Vandooren, M. (1958). Réflexions sur trois contusions thoraciques graves. *Poumon*, **14**, 173.

Virshup, M. (1960). The anteriorly crushed chest or 'steering-wheel injury'. *J. thorac. Surg.*, **39**, 579.

Westermark, N. (1941). A roentgenological investigation into traumatic lung changes arisen through blunt violence to the thorax. *Acta radiol.*, **22**, 331.

Wilson, J. V. (1943). The pathology of closed injuries of the chest. *Brit. med. J.*, **1**, 470.

Zenker, R. (1956). Die geschlossenen und offenen Verletzungen der Lunge und des Brustfells. *Arch. klin. Chir.*, **284**, 152.

OSTEOMYELITIS OF THE PREMAXILLA*

BY

E. C. ALLIBONE and C. P. MILLS

From the General Infirmary, Leeds

(RECEIVED FOR PUBLICATION FEBRUARY 21, 1961)

The superior maxilla forms the basis of the upper jaw. Osteomyelitis in this bone is a rare occurrence. Cavanagh (1960) found 152 cases in the literature but was able to add 24 of her own.

Most cases occur in the first three months of life. While the route of entry of the staphylococcus is disputed, the infection, once established, becomes widespread. Abscesses in relation to the floor of the orbit appear at the outer or inner canthi. Downward spread through the alveolus points in the region of the first deciduous molar tooth. Backward spread ruptures into the antrum and so drains into the nose. The clinical picture is that of an acutely ill feverish infant with a unilateral swelling of the face and eye, a swollen gum and a purulent nasal discharge all on the same side.

Osteomyelitis can, however, develop in relation to the upper incisor teeth, that is in the premaxillary portion of the superior maxilla. When this occurs the clinical picture is more localized and more benign. This observation is well known on the continent of Europe (Rickham, 1960). Grob (1957) mentions that in infants with complete hare-lip and cleft palate a much less virulent form of osteomyelitis is seen in the premaxilla.

Case Reports

Case 1. A twin, born in hospital, had thrived normally. In the second week of life he began to possett blood. By the end of the week the mother noticed a swelling of the upper gum on the right side. The same evening a tooth was noticed in the swelling as something white. Two days later the tooth came away, the swelling went down, but a discharging sinus persisted. While the gum was swollen the baby vomited frequently and had difficulty in sucking. Treatment was given at home by the general practitioner with oral penicillin.

At 3 weeks of age the baby was referred to the outpatient clinic. He appeared to be well. At the position of the right upper lateral incisor was a lentil sized granuloma. There was a little inspissated pus in the right nostril. The airway appeared to be clear. When seen 10 days later a purulent nasal discharge had developed from which *Staphylococcus aureus* resistant to penicillin was cultured. After a further 10 days the baby sneezed out of the right nostril a sequestrum about the size of the erupted tooth (Fig. 1). After this episode local antiseptic treatment was stopped in favour of oral erythromycin which was given for three weeks. During this time the nasal discharge dried up. Recovery was uneventful. The remaining incisor teeth subsequently erupted normally.

Case 2. A triplet, whose mother was English and father Jamaican, was born in hospital, birth weight 5 lb. 1 oz. She did not gain weight quite so quickly as her two sibs and vomited about once a day for no discernible reason. At the age of 3 weeks the mother noticed spots of blood sometimes on the cheek and sometimes on the nightdress. The baby was admitted on the 25th day for general reasons. She continued to vomit readily and did not gain weight. At the age of 6 weeks she became feverish and the right side of the face swelled up. The next day pus was noticed to be oozing from the upper gum margin. Culture gave a growth of *Staphylococcus aureus* insensitive to penicillin. Erythromycin and novobiocin were given orally for eight weeks and then, after a three-week interval, for a further five weeks. The initial fever settled after a

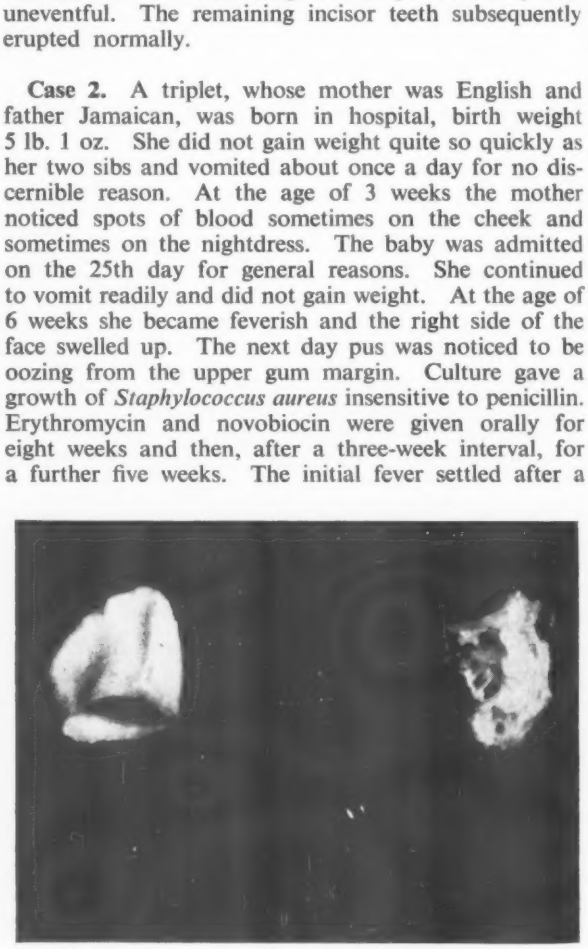


FIG. 1.—Case 1: The erupted tooth and the sequestrum which was subsequently extruded through the nostril.

* A paper read at a meeting of the Paediatric Societies of the Birmingham, Leeds, Liverpool and Sheffield regions held in Leeds in October 1960.

FIG. 2.—Case 2: The partially extruded and devitalized lateral incisor with delayed eruption of the central incisor of the same side. Condition at the age of 1 year.

few days. Two weeks later the right upper lateral incisor erupted and descended about half way. The baby thrived slowly. She still vomited readily.

At the age of 1 year the right upper lateral incisor was still in the same position. It was discoloured. Both left upper incisors had descended. The right upper central incisor had just cut the gum (Fig. 2).

Case 3. Paul H. was born in hospital. On arrival home on the 10th day the mother noticed an abscess on the upper gum which discharged pus from time to time. At the age of 3 weeks an 'abscess' appeared in the right nostril which was treated with oral penicillin by his family doctor. About this time the right eye became swollen and closed. Because of persistence of symptoms and some difficulty in breathing he was referred at the age of 5 weeks to a paediatric clinic. On examination he was pale but not toxic. There was a sanguinous discharge down the right nostril. The cheek and the right side of the nose were slightly swollen and there was a prominence the size of a pea near the inner canthus. The gums were not swollen, but the right upper central incisor was just visible (Fig. 3).

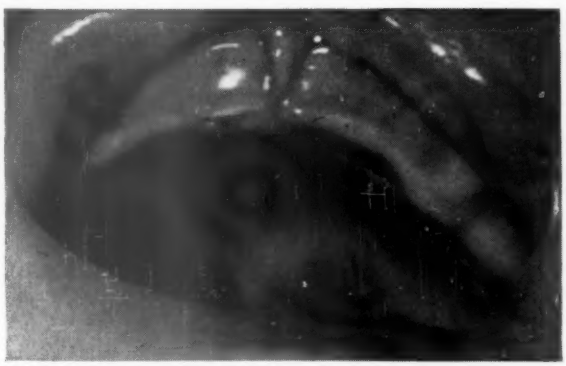


FIG. 3.—Case 3: Premature eruption of the right upper central incisor at the age of 5 weeks.

He was admitted to hospital. *Staphylococcus aureus* resistant to penicillin was cultured from nose and throat. He was treated with erythromycin and novobiocin for eight weeks. Because the swelling of the face and the nasal discharge persisted he was examined under anaesthesia. A sinus was found in the floor of the nose. The partially erupted incisor was lying in a bed of pus. It was extracted to facilitate drainage. He was then discharged.

He remained well. The haemorrhagic discharge from the nose persisted intermittently. When it stopped the swelling of the inner canthus became more noticeable and discharged. By the age of 5 months the right upper lateral incisor had erupted, but it came down crooked.

Discussion

The three cases described are similar in their presentation in early infancy as a swelling of the alveolus over one of the upper incisor teeth with subsequent eruption of the relevant tooth. In the first two cases the infection remained limited to the premaxilla. In the third case there was evidence of spread after the lapse of a week. The organism was in each case *Staphylococcus aureus*, coagulase positive and resistant to penicillin. The systemic reaction was slight.

The involvement of the premaxilla does not support the theory that osteomyelitis of the maxilla starts as an infection of the antrum. That in each case only one tooth bud was completely devitalized favours the concept that the infection settles in a tooth bud (Wilensky, 1932; Asherson, 1939; McCash and Rowe, 1953; Gregson, 1958).

The occurrence of hare-lip and cleft palate indicates a failure of fusion in the embryo of the maxillary and fronto-nasal processes. At birth there is normally no evidence of cleavage. Nevertheless, the tendency for infection to remain localized to the premaxilla in the above cases suggests the existence of a vascular watershed which forms a functional barrier to the spread of infection.

Summary

Three cases of osteomyelitis arising in the premaxilla are described. The clinical picture is contrasted with infection starting in the main portion of the maxilla.

We are greatly indebted to Mr. S. R. Fell, F.D.S.R.C.S., and to Mr. D. Jackson, D.D.S., for their help and advice.

REFERENCES

Asherson, N. (1939). Acute osteomyelitis of the superior maxilla in young infants. *J. Laryng.*, **54**, 691.

Cavanagh, F. (1960). Osteomyelitis of the superior maxilla in infants. A report on 24 personally treated cases. *Brit. med. J.*, 1, 468.
Gregson, A. E. W. (1958). Acute osteomyelitis of the maxilla in infants. *J. Laryng.*, 72, 312.
Grob, M. (1957). *Lehrbuch der Kinderchirurgie*, p. 114. Thieme, Stuttgart.
McCash, C. R. and Rowe, N. L. (1953). Acute osteomyelitis of the maxilla in infancy. *J. Bone Jt Surg.*, 35B, 22.
Rickham, P. P. (1960). Personal communication.
Wilensky, A. O. (1932). The pathogenesis and treatment of acute osteomyelitis of the jaws in nurslings and in infants. *Amer. J. Dis. Child.*, 43, 431.

AN UNUSUAL AORTIC ANEURYSM IN AN INFANT

BY

A. M. WOMACK and B. WOLMAN

From Bury General Hospital

(RECEIVED FOR PUBLICATION FEBRUARY 18, 1961)

Aortic aneurysm in infancy is very rare. Excluding examples of aneurysm of the ductus arteriosus in the newborn, we have been able to find only three previously reported cases, all of which were associated with congenital heart disease (Traisman and Johnson, 1953; Hartwell and Ewing, 1954; Rainey and Gilbert, 1958).

This appears to be the first recorded case of aortic aneurysm occurring in infancy as an isolated lesion.

Case Report

A female infant had been born after a normal delivery on October 10, 1959 with a birth weight of 6 lb. 1 oz. The mother had contracted 'influenza' with fever and malaise at the seventh month, but was said to be fully recovered after three weeks, thereafter having a normal confinement. The baby appeared normal after birth and had been fed on artificial milk feeds and made good progress, although she was reported to be a slow feeder.

At the beginning of February 1960, the mother was admitted to another hospital with suspected pneumonia, but was found to have pleural effusion. Her Mantoux test was positive and fluid aspirated from the lung was the typical straw-coloured lymphocytic fluid associated with tuberculous infection, but culture and guinea-pig inoculation gave negative results.

The baby was placed in the care of a foster mother who rushed her to the casualty department on February 17, 1960. The baby had been rather snuffly on the previous day and had suddenly gone pale, started to scream and seemed to have difficulty in breathing.

On admission, she appeared extremely ill, with gasping respiration, marked pallor and a cyanotic tinge to the lips. Her temperature was 99·6° F. and the heart rate was 160 per minute. The heart appeared to be normal in size and there was no audible murmur. Femoral pulses were not palpable. The liver was easily palpable, 2 to 3 cm. below the costal margin. There were basal moist sounds in both lungs but no peripheral oedema.

A tentative diagnosis of congenital heart disease with congestive failure, precipitated by respiratory infection, was made.

Despite treatment with digitalis and penicillin in an oxygen tent, the baby died about three hours after admission.

Autopsy Findings. The body was that of a well-nourished female infant weighing 3,800 g. and showing no external abnormality apart from cyanosis of the extremities.

The abnormal findings were confined to the thoracic cavity.

The pericardium was normal. The heart (32 g.) was not enlarged and the myocardium appeared normal. The heart valves were normal and there was no endocarditis. The foramen ovale was closed and the ductus arteriosus was obliterated. There were no congenital abnormalities of the heart or great vessels.

In the postero-medial aspect of the upper part of the descending thoracic aorta, a short distance below the obliterated ductus arteriosus, there was an oval hole 8 mm. in diameter, with a smooth, sharply-defined edge (Fig. 1). Through this defect, the aorta communicated with an aneurysmal sac 5 cm. in diameter, the endothelial lining of the vessel appearing to line the first 3-4 mm. of the neck of the sac; otherwise the wall of the sac appeared to be composed of laminated blood clot. The aneurysm occupied the upper part of the posterior mediastinum, compressing the left main bronchus and displacing the oesophagus to the left (Fig. 3). Attached to the intima of the aorta immediately below the oval defect, there was a firm, purplish-red nodule 0·5 cm. in diameter (Fig. 2). The remainder of the aorta was normal and there were no abnormalities in the peripheral vessels.

The anterior aspects of the left upper lobe and right middle lobe were pink and well expanded; otherwise the lungs showed large purple areas of collapse, which were confluent in the left lower lobe.

Histological examination of the aorta revealed no evidence of medial degeneration or loss of elastic tissue, and the only abnormalities were confined to the immediate vicinity of the aneurysm. At the edge of the opening into the aneurysm the muscle and elastic fibres were reflected into the neck of the sac, gradually to merge with and be lost in the organizing blood clot which comprised the major portion of the sac wall. The intimal nodule consisted of cellular fibrous tissue containing a few scattered inflammatory cells, and a few small areas of fibrinoid material (Fig. 4). No micro-organisms were seen.

The lungs showed large areas of collapse, with surrounding compensatory emphysema and many of the

FIG. 1.—Part of the postero-medial aspect of the aneurysm has been removed to allow the specimen to be flat.

FIG. 2.—Anterior view of the aneurysm with the aorta opened, showing the 'punched out' hole in the aorta and the intimal nodule.

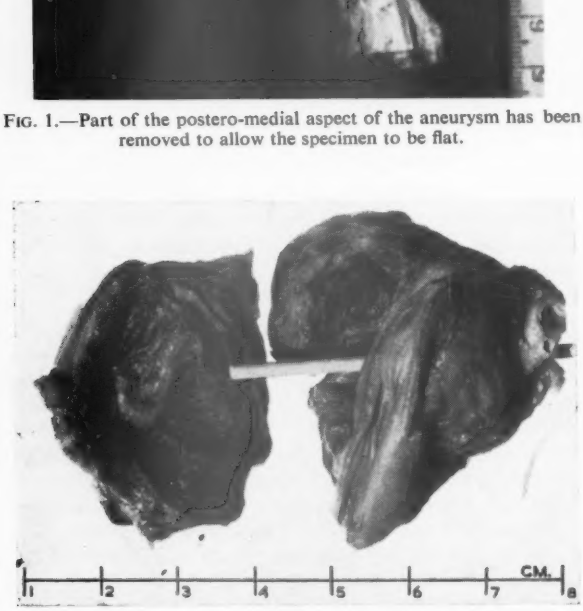


FIG. 3.—Posterior view of the aneurysm with part of the sac wall detached. The probe passes through the neck of the sac into the aorta. Note the stretched oesophagus.

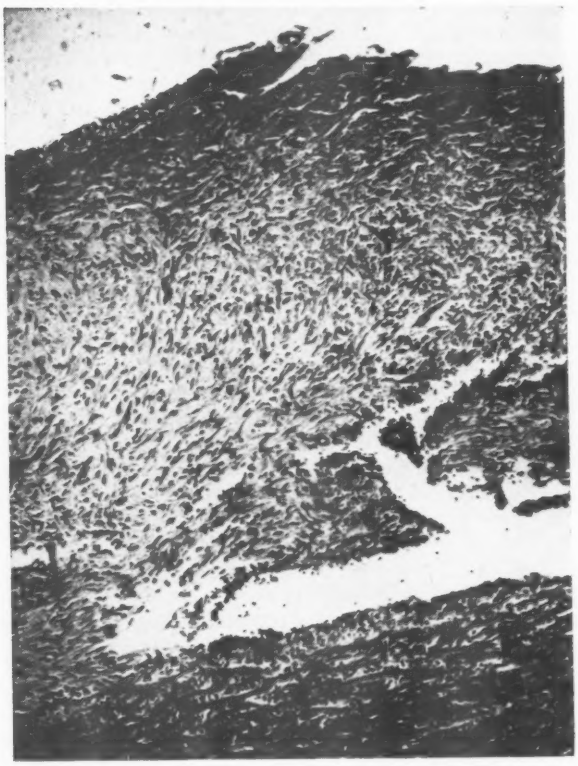


FIG. 4.—Photomicrograph of part of the intimal nodule. (Haemalum and eosin. × 38.)

alveoli and smaller bronchi contained inflammatory exudate. These changes were more marked in the lower lobes.

The liver showed slight passive venous congestion and fatty change.

No histological abnormality was seen in sections of myocardium, spleen, kidneys, adrenals and pancreas.

Discussion

In view of the age of this patient, it would be difficult to avoid the conclusion that this was a congenital aneurysm; but the word 'congenital' in this context does not necessarily denote a developmental abnormality.

Bronson and Sutherland (1918) gave five possible causes of aneurysm in childhood: (1) arteriosclerotic; (2) traumatic; (3) embolic (mycotic); (4) false (due to erosion from without); (5) congenital anomalies; to which list might be added: (6) polyarteritis nodosa.

In our case arteriosclerosis was not present, there was no history of trauma and nothing was found to suggest erosion of the aorta from without. Histological examination showed no evidence of polyarteritis nodosa. This leaves for further consideration two possible aetiological factors, i.e. mycotic and congenital developmental.

Analysis of those cases of congenital developmental aneurysm in which adequate details are given in the literature has revealed several distinctive features. These aneurysms are saccular or fusiform in shape, indicating a relatively large and diffuse weakening of the aortic wall, and are not infrequently associated with dissection. None have shown a relatively small 'punched out' defect as seen in the aorta in this case. Where histological examination of the aorta has been carried out, degenerative changes such as cystic medionecrosis or deficiencies of elastic tissue have been found. Furthermore, in the vast majority of adequately documented cases, congenital heart disease and frequently other congenital developmental anomalies have co-existed, coarctation of the aorta and Marfan's syndrome being among the more commonly associated abnormalities (Bronson and Sutherland, 1918; Calvin and Nichamin, 1934; Baer, Taussig and Oppenheimer, 1943; Schnitker and Bayer, 1944; Petch, 1952; Traisman and Johnson, 1953; Hartwell and Ewing, 1954; Whyte and Lu, 1956; Gulinati and Vita, 1957; Skandalakis, Edwards, Gray, Davis and Hopkins, 1960). Since none of these features existed in the present case, we would be reluctant to presume a congenital developmental aetiology unless the final possibility of a mycotic aneurysm had been excluded.

Only two cases of thoracic aorta aneurysm in children have been reported which structurally resemble that in our patient. Calvin and Nichamin (1934) described a similar aneurysm in a girl of 4 years, which had an oval opening with everted edges 8 mm. below the origin of the left subclavian artery. Near the lower edge of the hole were 'granular deposits', which, on microscopy, were seen to contain gram-positive cocci and diplococci, the diagnosis being 'verrucous streptococcic aortitis'. Javett and Kahn (1952) recorded a case in a child aged 2 years and 7 months in which death occurred after rupture of the aneurysm into a bronchus. This child had first been seen 18 months before death, suffering from non-haemolytic streptococcal septicaemia, at which time the chest radiograph was normal. The descriptions of these two aneurysms indicate a close similarity to the present case, and we consider it to be significant that in both cases there was evidence of a mycotic origin. The photomicrograph of the lesion in the aortic intima of Calvin and Nichamin's case is almost identical with the histological appearances of the nodule present in our case. We believe that it is justifiable to regard this nodule, the presence of which is otherwise difficult to explain, as a vegetation arising on the basis of a previous infective endarteritis.

Following the definition of Crane (1937) each of these aneurysms would be classified as a primary mycotic aneurysm: 'a lesion developing in the wall of an artery which is not associated with any demonstrable intravascular focus, as bacterial endocarditis, or with any in the surrounding tissue'. Such aneurysms are very rare, but published reports emphasize their predilection for the thoracic aorta (Revell, 1945; Javett and Kahn, 1952).

In considering the possibility of a mycotic origin, there remains the problem of the site of the original focus of infection. The infant appears to have thrived from birth, and did not ail at any time before the final fatal illness. It may also be thought that a maximum of four months is too short a time for such a lesion to develop from an infection acquired during extra-uterine life. However, the mother suffered from a febrile illness of three weeks' duration during the seventh month of her pregnancy, and it is not inconceivable that infection could have been transmitted transplacentally to the foetus at that time.

Potter (1952) believes the 'placental barrier' to infection to be greatly overrated and states that bacterial infections can be transmitted readily from mother to foetus, provided bacteraemia is present. In subacute bacterial endocarditis and endarteritis the tendency for infection to lodge where a stream

of blood impinges on normal endothelial surfaces is well recognized. When infection occurs in ventricular septal defect, the vegetations frequently develop on the wall of the right ventricle, and in patent ductus arteriosus they are most commonly seen at the pulmonary end of the ductus and on the opposite wall of the left pulmonary artery. The portion of the thoracic aorta immediately distal to the opening of the ductus arteriosus would therefore appear to be a favourable site for small infective emboli to become established during intra-uterine life.

Summary

An aneurysm of the thoracic aorta in a female infant causing death at the age of 4 months is described. The aetiology of the lesion is obscure but it is considered that the balance of evidence is in favour of presuming it to be a congenital mycotic aneurysm.

We wish to thank Miss J. Perry and Mr. R. Chadwick for the photographs.

References

Baer, R. W., Taussig, H. B. and Oppenheimer, E. H. (1943). Congenital aneurysmal dilatation of the aorta associated with arachnodactyly. *Bull. Johns Hopk. Hosp.*, **72**, 309.

Bronson, E. and Sutherland, G. A. (1918). Ruptured aortic aneurysms in childhood, with the report of a case. *Brit. J. Child. Dis.*, **15**, 241.

Calvin, J. K. and Nichamin, S. J. (1934). Thoracic aortic aneurysms in children. Their relation to rheumatic fever. *Amer. J. Dis. Child.*, **48**, 780.

Crane, A. R. (1937). Primary multilocular mycotic aneurysm of the aorta. *Arch. Path. (Chicago)*, **24**, 634.

Gulinati, G. C. and Vita, G. (1957). Ulteriore contribute alla rottura spontanea dell'aorta. *Arcisped. S. Anna Ferrara*, **10**, 1371.

Hartwell, A. S. and Ewing, G. M. (1954). Aneurysm of the thoracic aorta in infancy. *Postgrad. Med.*, **16**, 546.

Javett, S. N. and Kahn, E. (1952). Rupture of a mycotic aneurysm of the thoracic aorta. *Arch. Dis. Childh.*, **27**, 294.

Petch, C. P. (1952). Congenital aortic aneurysm with valvular stenosis and dissecting aneurysm. *Brit. Heart J.*, **14**, 147.

Potter, E. L. (1952). *Pathology of the Fetus and the Newborn*, pp. 105-6. The Year Book Publishers, Chicago.

Rainey, J. R., Jr. and Gilbert, E. F. (1958). Postductal coarctation of the aorta in an infant: case with aneurysms of aortic arch and anomalies of aortic arch system. *Tex. St. J. Med.*, **54**, 735.

Revell, S. T. R., Jr. (1945). Primary mycotic aneurysms. *Ann. intern. Med.*, **22**, 431.

Schnitker, M. A. and Bayer, C. A. (1944). Dissecting aneurysm of the aorta in young individuals particularly in association with pregnancy. With report of a case. *Ibid.*, **20**, 486.

Skandalakis, J. E., Edwards, B. F., Gray, S. W., Davis, B. M. and Hopkins, W. A. (1960). Coarctation of the aorta with aneurysm. *Int. Abstr. Surg.*, **111**, 307.

Traisman, H. S. and Johnson, F. R. (1953). Marfan's syndrome with aortic aneurysm. *Amer. J. Dis. Child.*, **85**, 706.

Whyte, D. and Lu, A. T. (1956). Coarctation of the aorta with aneurysm and rupture into the esophagus. Report of a case and review of the literature. *J. Pediat.*, **49**, 461.

A RARE TYPE OF CONGENITAL CYANOTIC HEART DISEASE

BY

PATRICIA FERNANDO and M. V. F. PERERA

From the Department of Paediatrics, University of Ceylon, and the Pathology Unit, Lady Ridgeway Hospital, Colombo

(RECEIVED FOR PUBLICATION DECEMBER 30, 1960)

A case of situs inversus with laevocardia and chamber inversion complicated by transposition and hypoplasia of the pulmonary artery and a patent ductus is published because of the rarity and complexity of this type of case. Advances in anaesthesiology and cardiac surgery demand that every case of congenital heart disease be subject to careful diagnostic appraisal in order that corrective surgery be effected where this is indicated. Where all the modern investigatory methods are available most of the congenital cardiac anomalies can be unravelled, but even under these circumstances a few bizarre anomalies defy accurate antemortem or pre-thoracotomy diagnosis. Unfortunately, our case died of intracranial abscess before we were able to complete even those investigations available to us, such as cardiac catheterization and blood gas analysis. Hence we had not reached a definite diagnosis when the patient came to autopsy.

Case Report

The patient, S.N., was a 9-year-old girl, who was admitted to the Children's Hospital, Colombo, on December 17, 1959, for fever of one week's duration, accompanied by vomiting during the latter five days. The fever had been heralded by chills and was intermittent. She did not complain of a headache, nor were there other clues in the history of this illness to suggest a diagnosis of a cerebral abscess. The parents' attention had been drawn to the child's cardiac anomaly by the school medical officer. They had not noticed cyanosis in early infancy. She had been admitted to the children's hospital five years previously for chest pain, but no further information about this illness could be obtained.

On examination, her nutrition was considered consistent with the low socio-economic status of her family, and her general condition was good. She was found to have clubbing of fingers and toes and central cyanosis.

No abnormalities were detected in the respiratory system.

The pulse rate was 98 per minute, the rhythm was regular and the volume and tension were good. Her blood pressure was 110/80 mm./Hg in each arm. The apex beat which was palpated in the fifth interspace in the left mid-clavicular line was left ventricular in type. No thrills were felt and there was no parasternal heave. A grade 3 systolic murmur was heard best at the base and was conducted to the clavicles. It was also heard at the third left interspace. The pulmonary second sound was soft and single.

Radiologically the heart was found to be moderately enlarged with predominant enlargement of the right ventricle. Screening was not done as the radiology department was under repairs. However, the postero-anterior view revealed oligaemia of the left lung field, with normal to increased vascularity of the right lung field (Fig. 1).

The electrocardiogram showed biventricular enlargement, the left being the dominant chamber (Fig. 2). No definite diagnosis was made about the condition for which admission was sought but, as her symptoms were relieved by the penicillin which was prescribed for her and because of the pressure for beds, she was discharged with advice to report back on January 2, 1960, so that her case could be discussed at the Cardiology Conference scheduled for January 5, of that year, when further cardiological investigations would be arranged.

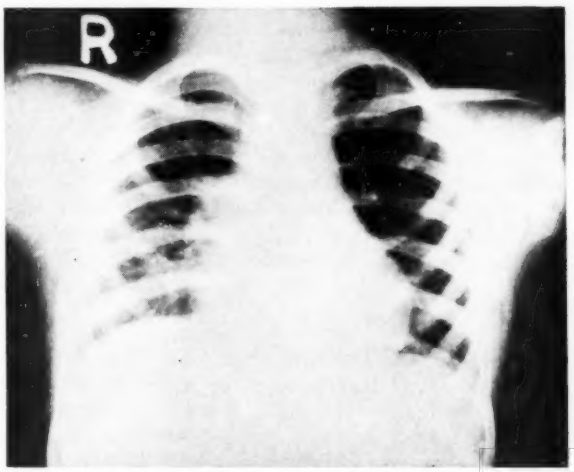


FIG. 1.—Postero-anterior teleradiograph.

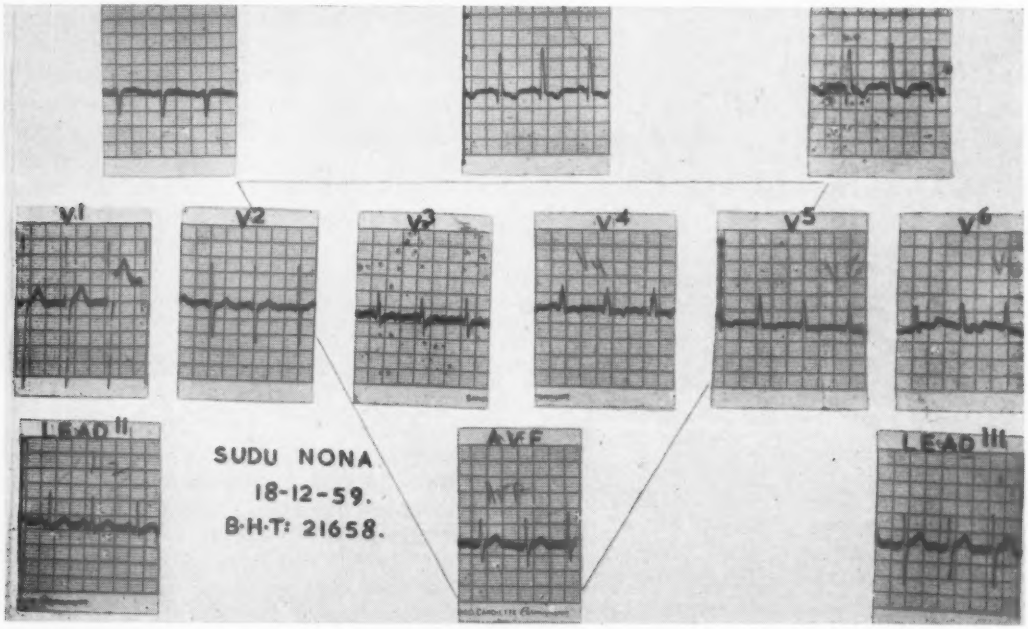


FIG. 2.—Electrocardiogram showing biventricular enlargement.

We were only able to say that she had bizarre anomalies of which we had spotted only the ventriculo-septal defect, pulmonary stenosis and hypoplasia of the left pulmonary artery. The cause of the cyanosis was still an enigma.

However, due to recurrence of vomiting severe enough to cause anuria and severe headache, she was readmitted on December 26, 1959.

On examination, we found a drowsy child who on being roused was very uncooperative. The cardiac findings were in *status quo* except for the pulse which was noted to be slow and bounding, leading to a suspicion of increased intracranial pressure. This was confirmed by the presence of bilateral papilloedema. We also noted marked pulsatile distension of the left-sided neck veins and this made us suspect a superior vena cava opening into the left atrium and thus accounting for the cyanosis. We made a tentative diagnosis of brain abscess, and treated her with pencillin and streptomycin in adequate dosage and with measures to reduce intracranial tension. Neurological examination carried out a few days later, when her mental condition permitted, pointed to a lesion in the posterior cranial fossa, i.e. bilateral extensor plantar reflexes and a tendency of the right arm to fall away to the same side.

An appointment for an electroencephalogram was made after consultation with the Neurologist, General Hospital, Colombo.

The parents removed the child against medical advice on January 16. At the time of discharge she had only minimal neurological symptoms or signs.

She was readmitted for the last time on February 16, with the same symptoms as on the previous occasion. She had marked papilloedema and her blood pressure had gone up to 130/95 mm./Hg. Hence she was put back on the previous therapeutic regime. A consultation with the Neurosurgeon, General Hospital, Colombo, was made and a transfer to the neurosurgical ward was advised. However, she died quite suddenly that night.

An autopsy was performed next morning and a right-sided cerebellar abscess was found (Fig. 3). It contained

FIG. 3.—Ventral surface of brain showing abscess of right cerebellar hemisphere.

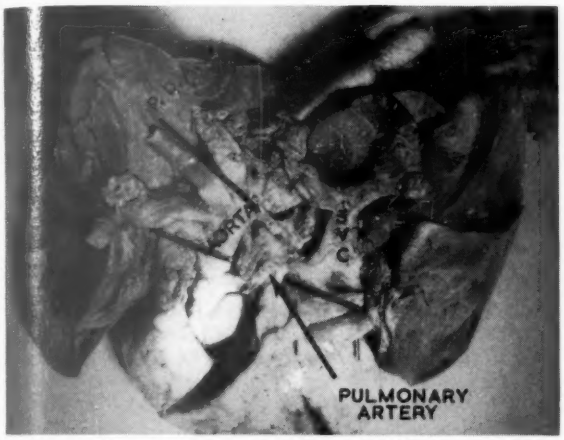


FIG. 4.—Anterior view of heart showing patent ductus arteriosus between aorta and left pulmonary artery, the left-sided superior vena cava and the transposition and hypoplasia of the pulmonary artery.

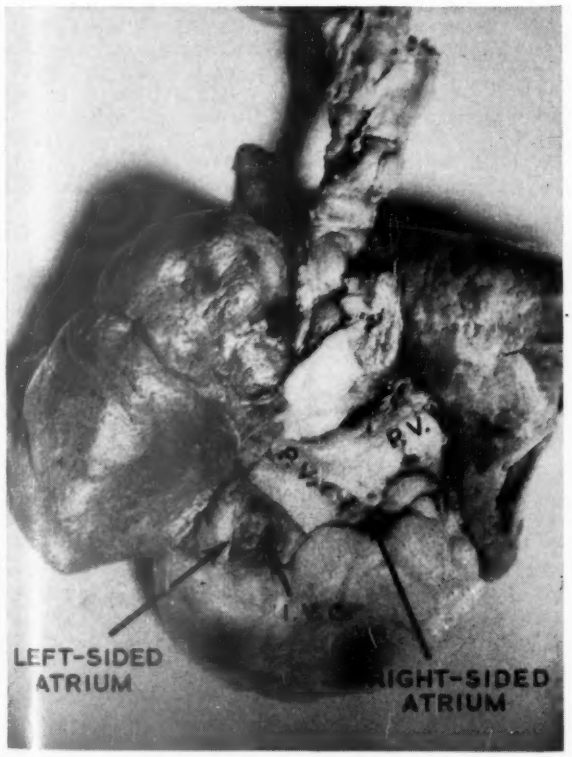


FIG. 5.—Posterior view of heart showing pulmonary veins [PV] opening into right-sided atrium and the opening of the inferior vena cava.

greenish yellow pus. There was a left-sided superior vena cava with gross enlargement of the right innominate vein as it crossed over and also definite dilatation of the left internal and external jugular veins. The heart was squarish in outline with the interventricular groove about midway (Figs. 4 and 5).

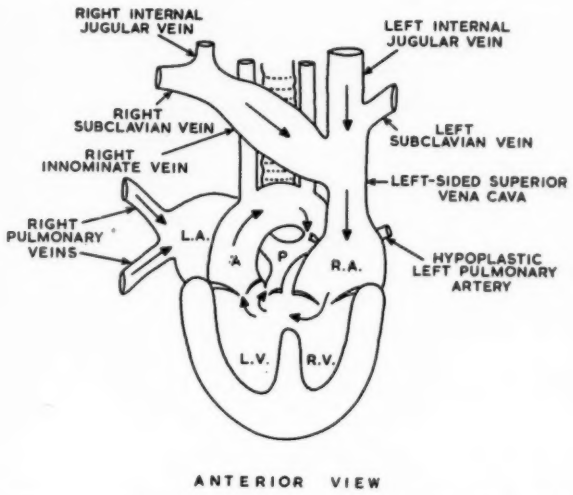


FIG. 6.—Diagrammatic representation of the cardiovascular anomalies.

The aorta and a small pulmonary artery were seen to arise from the right-sided ventricle, which communicated above with an auricle receiving all the pulmonary veins. A tricuspid valve separated these two chambers.

Situs inversus of lungs and abdominal viscera, not suspected during life, was found.

The inferior vena cava and the left-sided superior vena cava opened into the auricle on the left side, which was thus functionally a right auricle. However, this opened into a ventricle with muscular walls, the valve between these two chambers consisting of two long cusps and thus resembling the mitral valve. A large vessel did not arise from this ventricle, but there was a high septal defect between the two ventricles, the small pulmonary artery being immediately to the right of the septal defect. The left-sided ventricular wall was slightly thicker than the right-sided one, 12 mm. and 10 mm. respectively.

There was a hypoplastic left pulmonary artery as suspected during life from the radiologically evident oligaemia of the left lung field. A small patent ductus arteriosus was found between it and the aorta beyond the origin of the left subclavian artery. Fig. 6 is a diagrammatic representation of all the anomalies found. The cardiac chambers have been labelled according to their functional status and not according to the position in the body.

Discussion

According to Taussig (1947) situs inversus of the abdominal viscera with the heart occupying its normal position means that there has been complete reversal of all the organs and that the heart has been rotated back to the left. Such a condition is described as situs inversus with laevocardia. By laevocardia is meant that the heart is in the left hemithorax with the apex pointing to the left. She states that complicated cardiac anomalies

accompany situs inversus with laevocardia, and that accurate clinical diagnosis is extremely difficult. Nadas (1957) is in agreement with her and adds that asplenia may further complicate the picture.

Incidence. Keith, Rowe and Vlad (1958) estimate the frequency as approximately one-tenth that of situs inversus with dextrocardia which has been found in approximately one in 10,000 (Torgersen, 1949, 1950; Lowe and McKeown, 1954).

Campbell and Forgacs (1953) in reporting 14 of their own cases had found 19 more in the medical literature. Nadas mentions that 11 cases were encountered amongst cardiology cases at the Children's Medical Centre in Boston in the 10 years preceding the publication of his book, *Pediatric Cardiology*.

Pathogenesis. According to Forgacs (1947) it is the change in relation between the liver and the heart that is responsible for the venous drainage into the left rather than the right side of the heart and for the consequent abnormalities in septation and the development of the cono-truncus structures.

The insult responsible for this type of developmental abnormality probably occurs between the third and fourth embryonic weeks.

In our case the ventricular division is not only incomplete, but the division of the bulbus cordis into aorta and pulmonary artery has been unequal, resulting in a small pulmonary artery which, in addition, is transposed and arises from the same chamber as the aorta.

Circulatory Dynamics. The venous return from the upper and lower parts of the body which reaches the left-sided ventricle can leave it only through the septal defect and gains the arterial chamber where admixture occurs. Most of this mixed blood leaves this chamber via the aorta. Most of the blood reaching the small pulmonary artery reaches the right lung, the left lung receiving blood via the small patent ductus which connects the aorta and the left pulmonary artery. The entire venous return from the lungs reaches the functional left auricle.

We are grateful to Professor C. C. de Silva, under whose care this case was admitted, for permission to publish this case, and to Mr. A. T. S. Paul, Thoracic Surgeon, Dr. G. Ratnavale and Mr. S. A. Cabraal, Consultant Neurologist and Neurosurgeon, General Hospital, Colombo, respectively, for interest shown in this patient.

We are also deeply indebted to Drs. R. E. Bonham Carter and Martin Bodian of The Hospital for Sick Children, Great Ormond Street, London, who very kindly gave an opinion on the interpretation of the clinical and autopsy findings as depicted in our notes, radiographs, electrocardiogram and photographs.

We also extend our thanks to Dr. D. T. D. Bulugahapitiya, Research Assistant, Department of Paediatrics, for help given in the care of this patient, and to Messrs. P. D. S. Amarasekera and A. S. Mahawatte of the Photographic Department, University of Ceylon.

References

Campbell, M. and Forgacs, P. (1953). Laevocardia with transposition of the abdominal viscera. *Brit. Heart J.*, **15**, 401.

Forgacs, P. (1947). Congenital heart disease with isolated inversion of the abdominal viscera. *Ibid.*, **9**, 27.

Keith, J. D., Rowe, R. D. and Vlad, P. (1958). *Heart Disease in Infancy and Childhood*, p. 557. Macmillan, New York.

Lowe, C. R. and McKeown, T. (1954). An investigation of dextrocardia with and without transposition of abdominal viscera, with a report of a case in one monozygotic twin. *Ann. Eugen. (Lond.)*, **18**, 267.

Nadas, A. S. (1957). *Pediatric Cardiology*, p. 532. Saunders, Philadelphia and London.

Taussig, H. B. (1947). *Congenital Malformations of the Heart*, p. 513. The Commonwealth Fund, New York.

Torgersen, J. (1949). Genic factors in visceral asymmetry and in the development and pathologic changes of lungs, heart and abdominal organs. *Arch. Path. (Chicago)*, **47**, 566.

—— (1950). Situs inversus, asymmetry, and twinning. *Amer. J. hum. Genet.*, **2**, 361.

BOOK REVIEWS

Orthopaedia, Vols. 1 and 2. By NICOLAS ANDRY. (Pp. xiv + 540; 16 figures. 80s.) Philadelphia and Montreal: Lippincott; London: Pitman. 1961.

A facsimile reproduction of the first English edition (London, 1743) of Andry's famous book *L'Orthopédie*, this beautifully produced work, should interest all paediatricians as well as orthopaedic surgeons. Though Andry coined the word Orthopaedics he was not a mere mechanical operator. He was devoted to Child Health in all its aspects and concerned just as much with prevention as with cure. There are chapters on the causes and cure of dumbness, roughness of the hands, the body too thick or too slender, the King's Evil and bronchocele, piles, stitched stays and so on. As to the title, he says: 'I have formed it of two Greek words, *viz.* Ὀρθος, which signifies streight, free from Deformity, and παιδίου, a Child. Out of these two words I have compounded that of *Orthopaedia*, to express in one Term the Design I propose, which is to teach the different Methods of preventing and correcting the Deformities of Children.' He then describes some earlier work on similar subjects, and in one reference (which in the original text is printed as Kings 2, xxi, 20, when it should be Samuel 2, etc.), has perhaps the earliest account of what we now call the Laurence-Moon-Biedl syndrome. Like all orthopaedists, he had his favourite gadgets. He designed a chair which would prevent falling of the fundament, and upheld it against all objectors.

Among other treasures are: 'SHOES that are too high heeled will make the bodies of Children crooked and for this Reason they should go without them, especially Girls, till they are five years old.' 'The Method of preventing Children from pushing out the Backside too much . . . You must content yourself with reproving the Child frequently for the Fault; and to give the greater Force to those reproofs, you should not fail to mimick him frequently before his face.' 'The BODY too thick. This is a very great Deformity, especially in young Women.' The cure: 'To abstain from Chocolate, Beer and everything that is capable of producing too nourishing juices, and to eat and drink very moderately.'

On 'The BODY too slender' Andry anticipated not only the paediatrician with his not-to-worry attitude, but also the psychiatrist. 'Too lean a Body is a Deformity which we have less Cause to be alarmed at in Infants than when it is too fat. Children, at a certain time, necessarily grow lean, *viz.* when they begin to increase sensibly in their Growth. This leanness ought to give us no manner of Concern, for it is only for a Season. But there is another kind of Leanness, into which Children sometimes fall by certain secret Shagreens which they take. For the most part you will find that it arises from People in the House showing more fondness for some other Child, which excites him to Jealousy. One cannot imagine how painfully sensible Children are of this Partiality; they conceal their taking it amiss, and keep it as a Secret not to be revealed; but you must guess at their Trouble.'

There are references to tetanus: 'A Wound received in the fore part of the Foot sometimes deprives the Jaw entirely of motion', and iatrogenic disease: 'We sometimes see young Persons affected with a Trembling of their Hands, which is generally owing to the bad Custom which Parents have of giving their Children Quicksilver Water, either to cure them, or preserve them from Worms.' He knows when to refrain from treatment. 'There are some Fevers in which the Lips become scabbed, which prognosticates a perfect Cure, and these scabs do not require any Remedy; for the best way is to let them quite alone, and they will go off with the Fever.' We can easily forgive him for his occasional use of mumbo-jumbo, as in the treatment of bronchocele: 'Take four Pieces of Cloth of different Colours, green excepted, a Bit of Sponge, and a Dozen of Wood-Lice, and burn all together,' when we read that he is ready to cast all such aside in the treatment of teething, as: 'If the Brains of a Hare, or the Blood of a Cock's Comb, and such like ridiculous Applications, have ever seemed to be of service in Teething, the Virtues ascribed to them have been merely the effect of Friction.'

This edition is produced by a photographic process and neatly bound. The title-page and original plates are accurately copied, and the text is perfectly legible. The publishers record their thanks to two Connecticut doctors, Beckett Howorth and Charles W. Goff, for initiating and developing the project of republishing this book, and we can endorse that sentiment heartily.

Handicapped Children. By JOHN D. KERSHAW. (Pp. x + 228. 21s.) London: Heinemann Medical Books. 1961.

This book should be read by all who are concerned with the welfare—medical, psychological, educational and social—of handicapped children. In fact, it would make absorbing reading for almost every intelligent layman. The English is lively, stimulating and sustains interest throughout. Dr. Kershaw is a master of the telling phrase and adept with the arresting sentence. How better could the tolerance and realistic approach of the healthy child be contrasted with the acquired intolerance, based on fear, of many adults than in the following sentence, 'a child who has a major epileptic fit in the middle of a tedious lesson in school will probably frighten the teacher, but his schoolfellows will be grateful to him for the diversion'. This book contains not only

a wealth of common sense and practical advice about the general management of all kinds of handicapped children, their parents and their workmates, it also includes excellent chapters on individual problems such as blindness, deafness, epilepsy, physical deformity, mental subnormality, psychological maladjustment and cerebral palsy. There are two valuable appendices on handicapped children in the less well-developed countries, and the handicapped child and the law. The relationships which could and should exist between hospital consultants, family doctors and the medical officers of local authorities are well described by one who has obviously mastered the art of human relationships. It is a pity this type of effort was not more often in evidence throughout the country. Indeed, the essential points of both principle and practice so ably set out by the author would be applicable in any reasonably advanced country throughout the world.

The purely technical aspects of the medical and surgical problems of handicapped children are not described in any detail. There are many good textbooks where such detailed information may be obtained. But there is an abundance of practical advice of the type so often absent from formal textbooks for those doctors, nurses, almoners, teachers and social workers whose duty and satisfaction it is to help the individual child in trouble. The psychological advice which is to be found on almost every page will probably be much more acceptable to the average reader than much of the work written by professional psychiatrists, if only because Dr. Kershaw writes in straightforward, intelligible and enjoyable English. Unlike many books of a non-technical nature it is completely free from the rather nauseating sentimentality which the subject of handicapped children seems so often to engender. It is also free from the almost fanatical and unjustifiable dogmatism which some well-meaning but scientifically untrained enthusiasts have brought to their subject. This book is warmly recommended to all who have any interest in the problems of handicapped children.

Paediatric X-ray Diagnosis. 4th ed. By JOHN CAFFEY. (Pp. xxvi + 1,236; 1,536 figures. 240s.) Chicago, Illinois: The Yearbook Publishers; London: Interscience Publishers. 1961.

This magnificent book, well known to all paediatricians and radiologists, appears in its 4th edition considerably enlarged and containing many alterations and much new material. Most notable is the new section of 70 pages on cardiology mainly given to congenital heart disease, and a big expansion of the section on radiology of the skull containing radiographs and diagrams to illustrate neurosurgical diagnostic methods. There are innumerable additional improvements and changes scattered throughout the book. The author has expanded the principle of explanatory diagrams used in conjunction with x-ray pictures which has made for greatly increased lucidity, and the text has been amplified and in many sections completely rewritten.

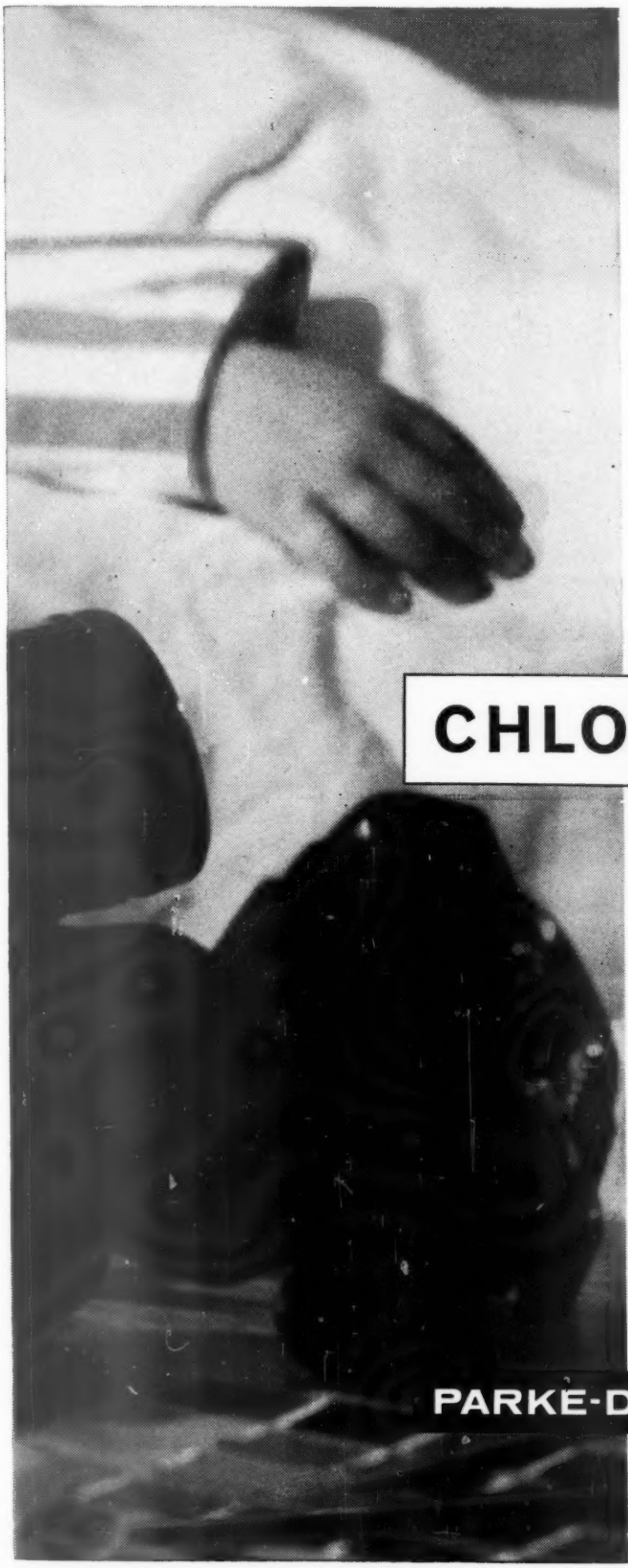
The preface to this edition contains a powerful plea for a reduction of radiation to the minimum possible. Dr. Caffey recommends economy in ordering radiographs a 'stingy' attitude in the x-ray department, a widespread use of image intensifiers and apparatus for reducing the amount of scatter and the abandoning of certain types of useless x-ray screening which he thinks is scarcely ever justifiable.

Dr. Caffey has very successfully brought his textbook up to date at a time when changes in paediatric radiology have been great. Though there are some omissions, for instance there is little about the specific changes in fibrocystic disease of the pancreas nor indeed about staphylococcal lung infection in general, and almost nothing about chronic pyelonephritis, on the whole the subject of paediatric radiology is handsomely and very adequately covered. Needless to say, the binding, printing and the quality of the reproductions are beyond reproach. This book must rank as one of the outstanding textbooks in the field of medicine.

Atlas der Normalen und Pathologischen Handskeletentwicklung. By FRANZ SCHMID and HELMUT MOLL. (Pp. iv + 114; 113 figures. DM. 78.) West Berlin: Springer-Verlag. 1960.

This book is meant as an atlas of the normal child's skeletal hand as it develops from birth to maturity, and as it is affected in pathological states. The x-ray appearances are shown for each quarter during the first year and annually thereafter and are amplified by detailed tables and charts. The variations from the norm are shown by two subsidiary radiographs of 'below' and 'above' normal without any indication of the range covered. The pathological section deals with variations from the normal, endocrine disturbances, disturbances of the metaphyses, nutritional and traumatic changes, but each section is very thinly covered and many conditions are completely ignored.

The binding, printing and quality of the reproductions are good and it is written in simple German. It is difficult, however, to understand the intention of the authors. The book is certainly too detailed for the paediatrician and yet does not cover its narrow field adequately enough to be considered a definitive textbook on the radiology of the hand during childhood.



put him quickly on the road to recovery

SUSPENSION

CHLOROMYCETIN

PALMITATE

A pleasantly-flavoured liquid preparation of Chloromycetin*, SUSPENSION CHLOROMYCETIN PALMITATE is indicated in staphylococcal pneumonia, in the early paroxysmal stage of pertussis, in bronchitis and bronchiectasis. Also effective in infantile gastroenteritis, acute otitis media and mastoiditis.

Each 4ml. teaspoonful contains the equivalent of 125 mg. chloramphenicol. Supplied in bottles of 60 ml.

PARKE-DAVIS

* TRADE MARK

PARKE, DAVIS & COMPANY. *Inc. USA Liability Limited*
HOUNSLOW · MIDDLESEX · TEL: HOUNSLOW 2361

THE BOY WHO NEVER SCORED A GOAL

He doesn't see himself as an international footballer. At the moment, not even as a footballer at all. Yet how he wishes he wasn't a "wheezy" child, and could join in!

Tedral is highly effective for the symptomatic relief of asthma. It is composed of theophylline, ephedrine hydrochloride and phenobarbitone, which ensures prompt and lasting relief.

It is easier—and pleasanter for the child—to administer flavoured Tedral Paediatric Suspension, of which each teaspoonful is equivalent to half a tablet of Tedral (the normal four-hourly dose for children aged 6 to 12). Tedral is also available in plain and enteric-coated tablets, the latter having a delayed action of 4 hours.

Tedral SUSPENSION

is available in bottles of 4 fluid ounces.

WILLIAM R. WARNER & CO. LTD.
EASTLEIGH, HAMPSHIRE. TELEPHONE: EASTLEIGH 3131.
TED 513

At the
nes he

thma.
e and
f.
nister
n tea-
ormal
s also
aving

131.
ED 513

AT

y

N

Vitamins in Prenatal Life

Vitamins are essential for the normal development of the embryo. Severe vitamin deficiencies during pregnancy, apart from their ill-effects on the mother, lead to death or malformation of the foetus. It is known from animal experiments that riboflavin is required in the later stages of bone development. Deformities which resemble human congenital malformations have also been observed following deficiencies of folic and pantothenic acids in the maternal diet. Although it is not possible to apply these results in detail to humans, adequate nutrition during pregnancy has long been considered to be of supreme importance.

Marmite is a useful source of every known factor of the vitamin B complex and is widely recommended to expectant mothers. Its appetising flavour ensures easy administration; it may be given as a drink made with boiling water or hot milk, or in sandwiches, or used in cooking.

MARMITE

yeast extract *contains* RIBOFLAVIN (*vitamin* B_2) 1.5 mg. per oz. NIACIN (*nicotinic acid*) 16.5 mg. per oz.

MARMITE LIMITED, 35 SEETHING LANE, LONDON, E.C.3

ADC 5608

STAPHYLOCOCCAL SUPERINFECTIONS

"Patients in hospital who have had an operation, and a course of 'broad—spectrum' antibiotics, sometimes develop diarrhoea which may be severe and even fatal."

Lancet Annotations 25th February, 1961

ENPAC

LACTOBACILLUS ACIDOPHILUS PREPARATION

For the prophylaxis and treatment of staphylococcal super infections.

"It was found that the staphylococci increased in both groups at the beginning of antibiotic treatment. Staphylococci continued to increase in the patients taking the antibiotic alone, but in those taking 'ENPAC' there was a pronounced drop in numbers."

Gordon D., Macrae J., & Wheater D. M. W. Lancet—May 4th, 1957. pp. 899-901

Samples and literature will be sent to the medical profession on request to:—

WILTS UNITED DAIRIES LIMITED · NUTRITION DEPARTMENT · TROWBRIDGE · WILTS